
# THERMOREGULATION IN ANOREXIA NERVOSA

April Chang

1983

Permission for photocopying or microfilming of "

Thermoregulation in Anorexia Nervosa

(title of thesis)

"

for the purpose of individual scholarly consultation or reference is hereby granted by the author. This permission is not to be interpreted as affecting publication of this work, or otherwise placing it in the public domain, and the author reserves all rights of ownership guaranteed under common law protection of unpublished manuscripts.

April Chang

(Signature of author)

April Chang

(Printed name)

2/3/83

(Date)

# THERMOREGULATION IN ANOREXIA NERVOSA

April Chang

A Thesis Submitted to the

Yale University School of Medicine

In Partial Fulfillment of the

Requirements for the Degree of

Doctor of Medicine

1983

ACKNOWLEDGEMENTS

During my four years at Yale Medical School, there have been many much appreciated individuals who have taken an active interest in my training and well-being. I wish to thank two of these people in particular, Ethan R. Nadel and Walter R. Anyan, my thesis advisors, for their countless hours of reading draft after draft, their advice, guidance, wisdom, encouragement, friendship, and sense of humor, especially during the frustrating and discouraging moments.

The assistance of Carol Walker, B.S. and Peter Jatlow, M.D. of the Department of Laboratory Medicine, James Virgulto, E.E. and Jacob Loke, M.D. of the Section of Pulmonary Medicine, Department of Internal Medicine, and C. Bruce Wenger, M.D., Ph.D., and Ms. Elise Low of the John B. Pierce Foundation Laboratory, for their chemical analyses of blood samples, determinations of residual lung volumes, constructive comments, and artwork have been appreciated. The support of these people and of the staff at the John B. Pierce Foundation Laboratory has made the completion of this project possible.

New Haven, Connecticut April Chang

December, 1982

ABSTRACT

Investigators have suggested generalized hypothalamic dysfunction in patients with anorexia nervosa. In order to test this hypothesis, five female outpatients with anorexia nervosa and five female control subjects exercised at an intensity between 40 and 50% maximal aerobic power ($\dot{V}O_2$ max) for 20 minutes on a cycle ergometer in an ambient temperature ($T_a$) of 33°C, and water vapor pressure of approximately 15 Torr. Metabolic rates and respiratory exchange ratios did not differ between the two groups; mean $\dot{V}O_2$ for the control group was 3.0 $ml \cdot min^{-1} \cdot kg^{-1}$ at rest and 22.6 $ml \cdot min^{-1} \cdot kg^{-1}$ at 15 minutes of exercise, and was 3.2 $ml \cdot min^{-1} \cdot kg^{-1}$ and 19.0 $ml \cdot min^{-1} \cdot kg^{-1}$ at 15 minutes of exercise for the anorectic group. The internal temperature ($T_{es}$) threshold for cutaneous vasodilation was elevated by 0.43°C in the anorectic group; vasodilation threshold $T_{es}$ was 36.91°C for the control group. However, the slope of the forearm blood flow (BF): $T_{es}$ relationship was unchanged; the mean slope was 20.8 ± 3.4 (SE) for the controls and was 13.2 ± 1.7 for the anorectic group. Mean $\overline{BF}$ and steady state $\overline{BF}$ was reduced by approximately 50% in the anorectic patients. Patients with anorexia nervosa thermoregulate, and the sensitivity of the peripheral thermoregulatory sensors is unchanged. The thermoregulatory responses of the anorectic patients are similar to those of hypovolemic subjects.

Mean percent body fat for five female anorectic patients was 6.9% by the skinfold thickness method and was 11.8% by body density determination. The skinfold thickness method is preferred, although it underestimates the true percent body fat since it does not measure

"deep" fat deposits nor fat amassed in breast tissue or in the gluteal region. The body density method is more cumbersome, and is affected by the gas volume in the gastrointestinal tract, the ability to maximally exhale when fully submerged, and the effects of starvation on muscle and bone mass.

INTRODUCTION

Early Descriptions:

The first medical description of anorexia nervosa, dated 1689, has been attributed to Richard Morton (10,46). In Phthisiologica: or a Treatise of Consumption, Morton describes a young woman who:

> In the month of July she fell into a total suppression of her Monthly Courses from a multitude of Cares and Passions of her Mind, but without any symptoms of the Green-Sickness following upon it. From which time her Appetite began to abate and her Digestion to be bad, her flesh also began to be flaccid and loose, and her looks pale...she was wont by her studying at Night, and continual pouring upon Books, to expose herself upon Day and Night to the injuries of the Air...I do not remember that I did ever in all my practice see one, that was conversant with the Living so much wasted with the greatest degree of Consumption (like a Skeleton only clad with Skin) yet there was no Fever, but on the contrary a coldness of the Whole Body....(10,46)

Sir William Gull described the disease as "hysteric apepsia" in 1868 (34), "anorexia hysterica" in 1873 (35) and finally in 1874 (36) he called it "anorexia nervosa". In 1888, Gull (37) described the symptoms of the disorder: emaciation associated with amenorrhea; constipation; loss of appetite; slow pulse and respiration; absence of somatic pathology; and persistent activity. Gull believed that the "origin is central and not peripheral. That mental states may destroy appetite is notorious." Concurrent with Gull's publications were those of Charles Lasèque who called the disorder "anorexie hysterique". In contrast to Gull's description of a "central origin", Lasèque preferred a "peripheral origin", initiated, for example, by an hysterical disturbance such as vomiting or abdominal pain.

The classical psychoanalytic theory of anorexia nervosa involves the expression of a sexual conflict--"oral impregnation" fantasies--as

described by Waller, Kaufman, and Deutsch in 1940 (75):

> The wish to be impregnated through the mouth, which results at times in compulsive eating, and at other times, in guilt and consequent rejection of food, the constipation of symbolizing the child in the abdomen and the amenorrhea as direct psychological repercussion of pregnancy fantasies. This amenorrhea may also be part of the direct denial of genital sexuality (20,41,52,61).

Other psychoanalysts stress the importance of the patient's personality, life style, ego functions, and interpersonal relations. The stereotypic patient with anorexia nervosa is often from an upper middle income family which is achievement oriented and superficially is "free" of problems or conflicts. The parents, however, are usually unfulfilled as a couple and seek fulfillment as individuals; for example, the mother through her children or the father through his career, and the child is wedged in between them as a buffer. Communication between family members is mundane and may center around food, weight, or physical appearance. One parent may become controlling, unaware of the child's individuality, and fearful of the separation which adolescence heralds. The child becomes achievement oriented and her self-image becomes dependent on external approval; self-determination and self-control do not develop to their potential. During adolescence, increased friction between parents, illness or death of a relative may initiate the disorder. An "ordinary" diet which has external approval becomes the patient's method of achieving self-determination and self-control.

Diagnosis and Assessment:

Bruch found the classical psychoanalytic explanations of anorexia nervosa and the tendency towards fitting anorexia nervosa into one of the contemporary psychiatric diagnostic categories to be inadequate and

therefore, she studied the patients' perceptual and conceptual disturbances (11,12). She classified three areas of disordered psychological functioning: 1) a disturbance of delusional proportions in the body image and body concept, with absence of concern and denial of thinness being pathognomonic; 2) a disturbance in the accuracy of perception or cognitive interpretation of stimuli arising in the body, expressed for example as, "I do not need to eat", decreased food intake, self-induced vomiting, bulimia, or overactivity and a denial of fatigue despite the lassitude, fatigue, and avoidance of activity found in undernutrition and chronic food deprivation; and 3) a paralyzing sense of ineffectiveness which pervades all thinking and activities. This last symptom, the sense of ineffectiveness, may be the crux of the disorder, hence much emphasis has been placed on this in psychotherapy (10,13).

Bruch also differentiates "atypical" anorexia nervosa and "psychogenic malnutrition" from "primary" anorexia nervosa (10,12). Psychogenic malnutrition is secondary to a number of disorders such as chronic schizophrenic reaction, acute catatonic schizophrenia, mental retardation, schizophrenic disorganization, and depression. Patients with atypical anorexia nervosa are concerned with their inability to eat (secondary to symbolic misinterpretations), complain about their weight loss, and do not pursue thinness except for coercive purposes or a desire to retain the sick or dependent role. This is in sharp contrast with the independent role which is sought by the patient with primary anorexia nervosa, the hallmarks of which have been aforementioned. The age of onset is not always easy to establish, but the patients with atypical anorexia nervosa are older, i.e., in their

twenties. On the other hand, primary anorexia nervosa affects adolescents, the majority of whom are female.

The third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) estimates that the disorder affects 1 in 250 females between the ages of 12 and 18 years (high-risk age group) and estimates that 95% of affected individuals are female (1). The diagnostic criteria (Table I) suggested by Feighner, et al. (24), in 1972 are more comprehensive than those listed in DSM-III and are used by a number of investigators (38,67,72,81).

TABLE 1. Diagnostic Criteria for Anorexia Nervosa

Age of onset before 25 years of age
Anorexia with accompanying weight loss of at least 25% of original body weight
A distorted attitude towards eating, food, or weight that overrides hunger, admonitions, reassurances, or threats with:
- Denial of illness
- Enjoyment in weight loss
- A desired body image of thinness
- Unusual hoarding or handling of food

No known medical illness that could account for the weight loss
No other known psychiatric disorder
At least two of the following:
- Amenorrhea
- Bradycardia: resting pulse of 60 or less
- Episodes of bulimia
- Emesis (may be self-induced)
- Lanugo
- Periods of overactivity

Anyan (2) assesses the patient's physical losses by determining a weight score which is a comparison between body weight and expected lean body mass: $\frac{\text{Body weight x 100}}{\text{expected LBM}}$. In girls, expected lean body mass is calculated from height using the following equation: expected LBM = $2.06\ e^{0.184\ \text{height}}$ in which LBM is in kilograms and height is in centimeters (27). In adolescent girls, the weight score is usually in the range between 119 and 138. When the weight scores are above the

range of 90 to 100, adipose stores are present. Patients with lower weight scores have a loss of lean body mass and there is depletion of the body's adipose tissue. Caliper measurements of skinfold thicknesses at the triceps, subscapular, pectoral, umbilical, iliac, and thigh regions are used to predict the percentage of fat in the body: $\frac{\text{Sum of 6 skinfolds (mm) - 8 mm}}{\text{Body weight (kg)}} \times 11.5$, where 8 mm is a correction factor for epidermal and dermal thicknesses. The range for nonobese girls is between 1.25 and 2.00 mm/kg (2). Stonehill and Nunnerley (70) compared skin thickness (measured radiographically) with skinfold thickness (measured with calipers) in patients with anorexia nervosa both pre- and post-treatment. They found that skin thickness did not change, but there was a significant increase in skinfold thickness post-treatment, reflecting the increase in subcutaneous fat with weight gain. Progressive loss of muscle mass can be followed with measurements of upper arm and thigh circumferences (2).

Physiology of Anorexia Nervosa:

Numerous etiologies of anorexia nervosa have been proposed, including lesions of the pituitary (Simmond's disease, first reported in 1914), hence the rationale for treatment with pituitary gland extracts (18). In 1930, Berkman reported low basal metabolic rate despite intact thyroid functioning. He described anorexia nervosa as a physiologic disorder secondary to a psychologic disorder in which pituitary insufficiency was secondary to a starved state and was reversible (5). Other findings associated with anorexia nervosa which are suggestive of hypothyroidism include constipation, dry skin, bradycardia, cold sensitivity, hypercholesterolemia, and hypercarotenemia.

Miyai, et al. (54), using radioimmunoassay techniques, measured thyroxine ($T_4$) and triiodothyronine ($T_3$) concentrations in the low normal range in patients with anorexia nervosa; however, others (55,67) have reported lower than normal levels of $T_3$. Thyrotropin (TSH) levels are considered to be normal (54,55,67); hence, low $T_3$ levels may not be perceived by the hypothalamus as a hypothyroid state. Boyar (7) reported normal to elevated concentrations of free thyroxine and suggested that the normal TSH may be appropriate for the level of "biologically active" thyroid hormone. Low $T_3$ levels unassociated with elevation of TSH concentrations have been found in the chronically ill (19) and with starvation (71), and may reflect regulation by metabolic demands and caloric deprivation. It is believed that the low $T_3$ concentration is secondary to decreased peripheral conversion of $T_4$ to $T_3$, and/or to increased conversion of $T_3$ to reverse $T_3$. The normal TSH concentration suggests that glandular secretion is normal (14). Moshang and Utiger (56) maintain that patients with anorexia nervosa are euthyroid, and that low $T_3$ concentrations and the "hypometabolic state" reflect a "homeostatic protective adjustment at the cellular level".

Cortisol levels have been measured by Warren and Vande Wiele (77) who demonstrated high plasma corticoids, low urinary 17-ketosteroids and 17-ketogenic steroids, and abnormal circadian secretory patterns for cortisol. This is in contrast with Boyar, et al., who found normal circadian secretory patterns (8) and later pointed out the necessity of multiple samplings in order to make conclusions regarding circadian rhythms (7). High plasma cortisol may be explained by abnormalities in cortisol binding capacity (17). Mecklenburg, et al. (50) evaluated

cortisol response to pyrogen or insulin-induced hypoglycemia and concluded that the hypothalamic-pituitary-adrenal axis was intact.

Another prominent finding in anorexia nervosa is amenorrhea, either primary or secondary, and this has led several investigators to study gonadotropin secretion. Boyar, et al. (9) studied nine patients with anorexia nervosa, six of whom had secondary amenorrhea and three of whom had primary amenorrhea, and measured plasma luteinizing hormone (LH) concentrations at 20-minute intervals for 24 hours. Eight of the nine demonstrated LH secretory patterns which were similar to those of prepubertal or premenarcheal girls. They suggested that a "regression" of LH secretory patterns occurs with secondary amenorrhea and that an "arrest" occurs with primary amenorrhea. Marshall and Fraser (49) reported low plasma LH levels which were unresponsive to clomiphene citrate (Clomid) until weight gain was achieved. This may not be an indication of pituitary dysfunction, but may merely reflect the observation that responsiveness to clomiphene citrate is acquired during middle to late puberty; hence, clomiphene citrate should not be used to treat patients with anorexia nervosa. Mecklenburg, et al. (50) infused LH releasing hormone (LHRH) in five patients with anorexia nervosa and found variable but normal LH and follicle stimulating hormone (FSH) responses in four of the patients, hence suggesting that pituitary gonadotropin synthesis and release were intact. Vigersky, et al. (73) infused 10 μg synthetic LH releasing factor (LRF) in girls with anorexia nervosa, simple weight loss, or normal weight, and found similar peak LH responses. These peak LH responses were delayed in the anorectic and simple weight loss groups. Peak FSH responses were greater in the underweight groups and response was delayed only in the

anorectic group. Hypothalamic dysfunction was suggested as an explanation for the delayed release of LH and FSH. This is in sharp contrast with Warren, et al. (77) and Sherman, et al. (68) who used younger subjects and larger doses of LHRH. Warren, et al. found that 50 μg LHRH infusions had minimal or no responses, but that secretion of LH and FSH in response to LHRH infusions became normal after weight gain. Sherman, et al. used 100 μg intramuscular injections of synthetic gonadotropin-releasing hormone (GnRH) in anorectic patients before, during, and after weight gain. When the patients were 53-64% of ideal body weight (IBW), the LH response but not the FSH response was impaired. At 79-88% of IBW, the LH response had improved but was still less than normal. Following maintenance of weight at 90-94% of IBW, the LH response was not significantly different from those of normal weight controls. They suggested that during malnutrition, there was either a decrease in the synthesis and/or storage of LH but not FSH secondary to independent regulation of the hormones, or differential sensitivities of the controlling mechanisms. Boyar (9) found that return to normal weight reverses the "regression" of LH secretory patterns.

Frisch and Revelle (31) hypothesize that a critical body weight triggers menarche by changing the metabolic rate which results in decreased estrogen sensitivity by the hypothalamus. This in turn resets the production level of gonadotropins and gonadal hormones for adequate amounts to initiate menarche. Malnutrition can delay menarche (32). Amenorrhea may result from chronic undernutrition but normal menstrual function may be restored following weight gain (43). Frisch and colleagues (30,33) have determined an index of fatness: $\frac{TW}{BWt}\%$ or a

"lean-fat ratio", where $\frac{TW}{BWt}\%$ = (100 - % fat) 0.72 and TW = total weight and BWt = body weight. Resumption and maintenance of menstrual cycles in women greater than 16 years of age requires an index of fatness of 56.1% which approximates 22% of the body weight as fat, and is approximately 10% heavier than the minimal weight for same height observed at menarche.

Warren (76) studied the effects of exercise on menarche and reproductive function in girls. She found that menarche was delayed in 13 ballet dancers whose mean body weight and calculated body fat were less than those of control subjects. Eleven of the 13 dancers developed secondary amenorrhea of at least 6 months duration which could not be attributed solely to weight, as they had percent body fat and mean weight within the range required for normal menstrual function as established by Frisch. Warren concluded that exercise constitutes an energy drain and can modulate body composition. Amenorrhea may be induced by the combined effects of this energy drain and dietary restrictions. Frisch, et al. (33) confirmed Warren's findings of delayed menarche and an increased incidence of secondary amenorrhea in ballet dancers secondary to their being below a critical body weight. This has also been demonstrated in swimmers and runners (23,29). Warren (76) suggested that delayed menarche and secondary amenorrhea are not entirely stress-related and cited, as examples, normal weight musicians who are training for professional careers.

Hypothalamic Dysfunction and Thermoregulation in Anorexia Nervosa:

In 1974, Mecklenburg, et al. (50), postulated hypothalamic dysfunction in the pathogenesis of anorexia nervosa although its sequential

relation with psychic stress and starvation could not be determined. Mecklenburg, et al. evaluated the hypothalamus using water conservation and thermoregulation as illustrative examples in five women with anorexia nervosa whose ages ranged from 19 to 43 years old, and the duration of the disease ranged from 1½ to 21 years. Water conservation was assessed by dehydrating the patient for 15 hours in four of the five patients, and 11 hours in one of the patients. Maximal urinary osmolalities after dehydration ranged from 387 to 820 mOsm/l with serum osmolalities ranging between 285 and 295 mOsm/l. Aqueous vasopressin (5 Units) was administered subcutaneously and urinary osmolalities ranged from 573 to 737 mOsm/l; the percent increases ranged from 13.1 to 48.1 and were interpreted as partial diabetes insipidus in four of the five patients. These results would have been better interpreted if the predehydration urine and serum osmolalities, 24-hour urine volumes, and urine specific gravities pre- and post-dehydration and after vasopressin administration had been obtained. Mecklenburg, et al. followed the protocol of Miller, et al. (51), who pointed out that tests in which the dehydration period is predetermined are subject to erroneous interpretation since the urine osmolality may not have reached a plateau prior to vasopressin injection. This frequently happens in patients with primary polydipsia who are overhydrated. Overhydration in patients with anorexia nervosa could occur in their attempts to hide weight loss. Fohlin (25) was unable to demonstrate any increase in maximal urinary osmolalities after administration of vasopressin; hence the abnormality may not be hypothalamic as proposed by Mecklenburg, but renal.

Mecklenburg, et al. (50) also studied thermoregulation by placing

subjects in the cold (10°C) and in the heat (49°C). Core temperature was measured at one-minute intervals using a rectal thermistor probe, and sweat rate was monitored by weight loss. The five patients with anorexia nervosa did not demonstrate the paradoxical response to cold by increasing their core temperature, i.e., via peripheral vasoconstriction and shivering; all had decreases in core temperature which did not stabilize, and none shivered detectably. In the heat, the patients stored greater amounts of heat. Four of the five patients with anorexia nervosa had normal sweat rates, however.

Jéquier (40), using direct calorimetry and thermometry, demonstrated that women with anorexia nervosa had lower heat losses per square meter of body surface area and a higher thermal body insulation than women of normal weight in ambient temperatures of 20° and 28°C. The body's thermal insulation is influenced by the amount of subcutaneous fat and the rate of subcutaneous (sic.) blood flow. In patients with anorexia nervosa, the subcutaneous fat insulation is lower, but the vasoconstriction insulation is greater. The largest insulation is seen at 28°C, secondary to intense vasoconstriction in the subcutaneous tissues. Luck and Wakeling (48) have proposed that increased cutaneous vasoreactivity to the cold is augmented by local sympathetic vasomotor activity and is unrelated to increased blood viscosity as seen in Raynaud's phenomenon. They did not, however, find maximal vasoconstriction at 28°C.

Jéquier's findings could explain Mecklenburg's (50) demonstration of the absence of a paradoxical increase in core temperature when patients with anorexia nervosa are exposed to the cold; the patients are maximally vasoconstricted at 28°C and despite lower heat losses per

square meter of body surface area than controls at 20°C, they may be unable to maintain a high body core temperature. In addition, the absence of shivering may be an adaptive strategy, as shivering thermogenesis is metabolically expensive (40,66) and anorexia nervosa patients do not have a large fuel reserve from which to draw.

Wakeling and Russell (74) studied the effects of immersing one arm up to the elbow in a water bath heated to 45°C on oral (sublingual) temperature and peripheral skin (finger) temperature of the other arm in eleven patients with anorexia nervosa. The ambient temperature was between 20 and 21°C. The heat stimulus was expected to increase the central (oral) temperature followed by a compensatory peripheral vasodilatory response. Resting oral temperatures were significantly lower in the patients (mean 36.1°C) than in the controls (37.05°C). Peripheral vasodilation was assumed to commence when the skin temperature increased 0.5°C from its baseline; at 33°C skin temperature, there was a plateau in the rate of rising peripheral skin temperature in response to the heat stimulus in the control subjects. Onset of vasodilation was delayed and occurred at a higher oral temperature (37.5°C) in the patients than in the controls (37.25°C), and the vasodilatory response was slower. When the patients regained approximately 90% of their "standard weight", their resting oral temperatures were still significantly lower (36.7°C) than the controls (37.05°C), but the temperature at which vasodilation occurred was not significantly different from the controls. They concluded that the thermoregulatory mechanisms were markedly impaired, i.e., there was decreased sensitivity to a heat stimulus, when the patients were severely malnourished. However, with an ambient temperature of approximately 20°C, the patients are vasocon-

stricted to increase their thermal body insulation (40) and it is unlikely that the heat stimulus of forearm immersion is a large enough stress to cause peripheral vasodilation except at a slow rate and at a higher core temperature.

Luck and Wakeling (47) modified Wakeling and Russell's (74) experimental design: oral (sublingual) and skin (mean of six sites) temperatures were measured when both calves were immersed in 42°C water in an ambient temperature of 20°C; forehead sweating was noted with the use of iodine-impregnated paper; and hand blood flow was measured with a simple water-filled venous occlusion plethysmograph. They found that the initial mean hand blood flow and the initial core temperature in 13 patients with anorexia nervosa were significantly less than in controls. Vasodilation in response to the heat stimulus occurred at significantly lower oral and peripheral temperatures (i.e., "shift to the left") although the rise in oral temperature required to initiate vasodilation was greater. There was no difference in the mean maximal blood flow rates. Sweating in patients with anorexia nervosa occurred at lower core and mean skin temperatures than in controls. This observation, however, may reflect an autonomic response to stress rather than represent thermoregulatory sweating. Luck and Wakeling concluded that the vasodilatory response was slower due to lower initial hand blood flow, and not secondary to decreased sensitivity to a heat stimulus as proposed by Wakeling and Russell (74) ten years earlier.

Fohlin (25) studied the effects of anorexia nervosa on physical and circulatory characteristics at rest, during exercise, and at maximal aerobic power ($\dot{V}O_2$ max). The girls demonstrated bradycardia at rest with a mean heart rate of 54 beats per minute (bpm). $\dot{V}O_2$ max was 32

$ml \cdot min^{-1} \cdot kg^{-1}$ and was lower than in control girls. Peripheral circulation was assessed by the effects of radiant heat on calf blood flow (measured with an air-filled venous occlusion plethysmograph) and found to be significantly reduced. Skin temperature was measured and found to be lower at five to six levels on the distal lower limb. After regaining weight, eight of the patients were restudied and resting heart rate and $\dot{V}O_2$ max had returned to normal at 79 bpm and 46 $ml \cdot min^{-1} \cdot kg^{-1}$, respectively. This work was represented in greater detail in subsequent papers (26,28).

Davies, Fohlin, and Thorén (21) investigated temperature regulation during prolonged exercise at approximately 65% $\dot{V}O_2$ max in patients with anorexia nervosa. They demonstrated that "preheating" the patient in a sauna or increasing the ambient temperature from $24^{o}$ to $32^{o}C$ raised the rectal temperature, but had little effect on the rate of change or the final temperature reached during exercise. It should be noted that these results were based only on two patients. When the ambient temperature was decreased to $12^{o}C$, the rectal temperature remained essentially constant during exercise. Absolute evaporative sweat loss was lower, but when compared to the total heat production, it was within the range of normal controls. Mean skin temperatures were higher in the patients after exercise in ambient temperatures of both $24^{o}$ and $32^{o}C$; the distribution, however, was different at $24^{o}C$, despite "preheating". They concluded that patients with anorexia nervosa regulated their core temperature similarly to those individuals who are extremely sedentary or unacclimatized. In the heat, the patients sweated, but had a decreased maximal capacity and stored more heat than controls. In moderate ambient temperatures ($24^{o}C$), the heat produced during exercise

was lost differently from controls, secondary to their low sweating capacity and peripheral vasoconstriction. They postulated that the heat was dissipated through a counter-current exchange mechanism and that there was no evidence for hypothalamic dysfunction regarding thermoregulation.

The primary concern of this investigation is the study of thermoregulatory mechanisms in patients with anorexia nervosa and the controversy regarding hypothalamic dysfunction. Part I of this study is the assessment of thermoregulation during exercise in the heat. Part II is a comparison of two methods of assessing adipose stores: skinfold thickness versus body density.

Subjects:

Five female outpatients with anorexia nervosa (mean physical characteristics: ht. 162 cm; wt. 41 kg; wt. score 102; age 18 yr), and five female control subjects (mean physical characteristics: ht. 161 cm; wt. 56 kg; wt. score 142; age 20 yr) (Table 2) were studied at the John B. Pierce Foundation Laboratory, New Haven, Connecticut, during August, 1980 (except patient L.S. who was studied during September, 1981). All subjects were studied following written informed consent by the subject, parent (required for subjects younger than 18 years of age), and physician. This protocol had been approved by the Human Investigations Committee of the Yale University School of Medicine (HIC #2146).

The patients met the diagnostic criteria suggested by Feighner, et al. (see Table 1 in Introduction) (24) and were under the care of Walter R. Anyan, M.D., at the Adolescent Clinic of Yale-New Haven Hospital. Dr. Anyan first suggested to the patients that they might consider participating in a research project. When a patient expressed interest, she was contacted in order to explain the goals and protocol of the study to her and her parent(s). Control subjects were recruited from the Hamden Hall Country Day School, Hamden, Connecticut with permission of Headmaster Richard Dolven, and from the Yale University community.

All subjects were invited to the laboratory to become familiarized with the procedures prior to the study, were encouraged to discuss the conditions of the experiment at any time, and were free to terminate

participation at any time during the experiment without adversely affecting payment for what had been completed or other interactions with the institution. All patients had notes placed in their hospital records, acknowledging their participation in this investigation.

Inherent in this study was selection bias, secondary to willingness to participate, physical condition, and with regard to patients' psychiatric condition. Hence, these subjects may not represent anorectics in the general population. Females were chosen since it has been estimated that 95% of affected individuals are female (1).

Part I: Thermoregulation during exercise in the heat

All subjects, dressed in shorts and top, were seated at rest in a contour chair behind the pedals of a modified Monark cycle ergometer (Figure 1) (6) for ten minutes at an ambient temperature of 33°C. The partial pressure of water vapor was approximately 15 Torr. After the rest period, the subjects exercised for 20 minutes at an intensity between 40 and 50% of maximal aerobic power ($\dot{V}O_2$ max). The intensity was determined from the heart rate response during a trial bout of exercise during the introductory session (4). Pedaling velocity was 60 rpm, achieved by the subjects' keeping time with a metronome. Intensity was adjusted by varying the tension imposed on a friction belt around the flywheel of the ergometer.

Internal temperature ($T_{es}$) was measured with an esophageal probe constructed of a polyethylene coated copper-constantan thermocouple. The differential in thermoelectric powers of the two metals creates a voltage between the two junctions, which was recorded. The thermocouple wire was referenced against melting ice and was calibrated at the end

of each experiment in a heated water bath with a Bureau of Standards thermometer accurate to 0.01°C. Subjects were trained to pass the thermocouple catheter beyond the nasopharynx to a length of one-fourth their height past the tip of the nose, placing the thermocouple tip at the level of the left atrium, as demonstrated radiographically in prior studies from this laboratory (78). At this level, the thermocouple is relatively insensitive to small displacements.

Skin temperatures were measured from thermocouples mounted across steel or plastic rings. The rings were attached to the skin at eight sites with the outer surface of the thermocouple freely exposed to the air. Mean skin temperature ($\overline{T}_{sk}$) was calculated as described by Wenger (79) once per minute using the following equation: $\overline{T}_{sk} = 0.115\ T_1 + 0.170\ T_2 + 0.205\ T_3 + 0.090\ T_4 + 0.080\ T_5 + 0.053\ T_6 + 0.190\ T_7 + 0.097\ T_8$; where 1 = chest, 2 = posterior flank, 3 = forehead, 4 = anterior flank, 5 = lateral upper left arm, 6 = left forearm, 7 = anterior thigh, and 8 = lateral calf. This weighting is based on the product of regional area and local relative thermal sensitivity.

Forearm blood flow was measured twice per minute by venous occlusion plethysmography using a Whitney mercury-in-Silastic strain gauge (Figure 2). The gauge, placed on the forearm, was constructed of a continuous thread of mercury within a length of Silastic tubing. The ends of the tubing were sealed with copper pins and as the tube was stretched or contracted, the resistance of the mercury thread was changed. The gauge formed one arm of a Wheatstone bridge and the change in voltage between the nodes of the bridge was recorded. This voltage has an almost linear relationship to the change in resistance, and hence to the change in length of the gauge (80). A venous occlusion cuff 3.5

cm wide was placed over the upper arm. A piece of flexible metal which was placed over the occlusion cuff kept the cuff flat against the skin, hence reducing the inflation time and offering better transmission of pressure to deeper tissues. The venous occlusion cuff was instantaneously inflated with air to a pressure of 30 Torr twice per minute during the initial ten minutes of exercise, and once per minute during the final ten minutes of exercise. Each inflation was maintained for 5-8 seconds. During the entire experiment, hand blood flow was occluded with a 3.5 cm pneumatic wrist cuff inflated to approximately 300 Torr which obliterated the radial pulse distally. When the pneumatic wrist cuff and venous occlusion cuff were simultaneously inflated, the forearm received blood from its own arterial supply, but not from the hand, and no blood could be drained proximally. The circumference, and therefore the volume, of the forearm increased during inflation of the venous occlusion cuff at a rate proportional to the rate of arterial blood flow. As this change in circumference stretched the strain gauge, the change in voltage was recorded. Slopes of tangents fitted on the plethysmographic records were determined and used to estimate forearm blood flow (Figure 3).

Forearm blood flow calculations were based on the assumption that the forearm is a cylinder and that all expansion is in the radial direction. Thus, the volume, V, of a forearm segment is $\pi r^2 \ell$, where r is the radius and $\ell$ is the length. $\frac{dV}{V} = \frac{2\pi r \ell \, dr}{\pi r^2 \ell}$ and $\frac{2dr}{r} = \frac{2dC}{C}$, where C is the forearm circumference measured at the site of the gauge immediately post-exercise. The strain gauge was calibrated around a plexiglas cylinder at the end of the experiment; voltage changes were recorded as the screw on the plastic portion of the strain gauge

adjusted the amount of stretch or contraction. The change in the Wheatstone bridge output (in volts) was divided by the number of the turns of the screw (pitch of 32 per inch) and multiplied by 32 to give X, the change in signal per inch change in length of the gauge:

$$X = \frac{a \text{ volts} + b \text{ volts}}{c \text{ turns} + d \text{ turns}} \times 32.$$

Slopes of the tangents (volts/min) were converted to milliliters of blood flow per 100 mililiters of tissue per minute by multiplying by:

$$\frac{200 \text{ ml}}{(100 \text{ ml})\ (C)\ (X)}.$$

The arms were pronated with flexion of the wrists and fingers. The arm was supported and suspended in this position at shoulder level in order to allow for adequate venous drainage when the venous occlusion cuff was deflated. Movement artifacts on the plethysmographic records were minimized as a result of having the subject seated in a contour chair behind the pedals and having her arm suspended from the ceiling; these supportive measures allowed relaxation of the trunk, and arm and shoulder girdles. During the exercise period, changes in forearm blood flow were interpreted as changes in skin blood flow over most of the body. Previous studies in passively heated subjects have demonstrated that forearm vasodilation is confined to the skin vasculature (65) and is considered an efficient thermoregulatory mechanism.

Oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were measured throughout the entire experiment. The external nares were occluded with nose clips. A mouthpiece was attached to a Collins triple-J low resistance one-way valve through which the subject inspired room air and expired air which was directed into a mixing chamber. Continuous sampling from the mixing chamber was achieved with a short length of polyethylene tubing which was connected to the

head of a Beckman LB-2 infrared analyzer for $CO_2$ analysis and a Beckman paramagnetic oxygen analyzer (Figure 4). Time delay of the entire system was less than three seconds. The gas analyzers were calibrated at the beginning and end of each experiment against gases of known concentrations (checked against gas chromatography).

Continuous recordings of the fractional concentrations of oxygen ($F_{EO_2}$) and carbon dioxide ($F_{ECO_2}$) and continuous recordings of the expired ventilatory volume ($\dot{V}_E$) were used to calculate oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and the respiratory exchange ratio (R) with the following equations:

$$\dot{V}O_2 = \dot{V}_E \left(1 - (F_{EO_2} + F_{ECO_2})/F_{IN_2}\right) F_{IO_2} - \dot{V}_E \left(F_{EO_2}\right);$$

$$\dot{V}CO_2 = (\dot{V}_E)\ (F_{ECO_2});$$ and

$R = \dot{V}CO_2/\dot{V}O_2$, where $\dot{V}O_2$ and $\dot{V}CO_2$ are in liters/min.

$\dot{V}O_2$ and $\dot{V}CO_2$ were corrected to STPD (standard temperature and pressure, dry) using standardized tables (16).

Peripheral venous blood samples were taken using a 20-gauge Vacutainer needle before commencing the ten minute rest period, and immediately post-exercise. The blood was analyzed for glucose, urea nitrogen, creatinine, triglycerides, and lactic acid by the Clinical Chemistry Department of Yale-New Haven Hospital. Subjects were in the post-absorptive state.

Part II: Assessment of adipose stores by two methods

Skinfold thicknesses at the triceps, subscapular, pectoral, umbilical, iliac, and thigh regions were obtained by Walter R. Anyan, M.D. using Lange calipers. Predicted percent body fat was calculated by: $\frac{\text{sum of 6 skinfolds (mm) - 8 mm}}{\text{Body weight (kg)}} \times 11.5$, where 8 mm is a correction

factor for epidermal and dermal thickness (2). A weight score was calculated by: $\frac{\text{Body weight x 100}}{\text{expected LBM}}$ (2), where the expected lean body mass (LBM) for girls was calculated by: expected LBM = $2.06\ e^{0.184\ \text{height}}$; LBM in kilograms and height in centimeters (27).

Estimation of specific gravity, using the Archimedian principle, was modified after Ricci (63) (Figure 5). The subjects were first weighed on a scale accurate to one gram. The subject then inserted a spirometer mouthpiece attached to a 15 cm plexiglas tube, and lay on a frame suspended from an autopsy-type scale above the water of a Hubbard tank. The frame was lowered into the water for complete submersion. When fully submerged, the subject was instructed to exhale completely and the weight was recorded. Underwater weights for six submersions were recorded and averaged. Calculations to determine percent body fat used equations from Keys and Brozek (42):

Body density = $\frac{\text{Body wt x density of water at } T_w}{\text{Body wt} - (\text{Underwater wt} + (\text{RV x density of water at } T_w))}$, where weight is in kilograms, RV is residual volume in liters, and the density of water at 37°C = 0.993. Percent body fat = $100 \times (\frac{5.120}{\text{sp.gr.}} - 4.684)$, where specific gravity (sp.gr.) = body density x 1.007; 1.007 is the relative volume of water at 37°C.

Residual volume is the volume of gas remaining in the lungs after a maximal expiration and was determined with body volume plethysmography. A body volume plethysmograph is a large air-tight box in which the subject sits (Figure 6). It has an opening in the wall through which gas is displaced when the subject changes volume; this volume is measured with a spirometer. Breathing is accomplished through a mouthpiece connected to the outside. At the end of expiration, the mouthpiece is occluded from the outside and the subject is instructed

to "pant like a puppy". This maneuver alternately expands and compresses the gas in her respiratory system; the gas pressure in the mouthpiece equals the lung gas pressure if the larynx is open. The difference in pressures between the mouthpiece and the atmosphere is displayed on the abscissa of an oscilloscope and the change in body volume measured by the plethysmograph is displayed on the ordinate. The total volume of gas can be calculated from Boyle's law: at a constant temperature, Pressure x Volume = a constant;

$$P_1V_1 = (P_1 + \Delta P)\ (V_1 + \Delta V);$$

$$P_1V_1 = P_1V_1 + \Delta VP_1 + \Delta PV_1 + \Delta P\Delta V.$$

Since $\Delta P\Delta V$ is miniscule hence,

$$0 = \Delta VP_1 + \Delta PV_1 \text{ and}$$

$$V_1 = -P_1 \frac{\Delta V}{\Delta P}\ .$$

In this case, $P_1$ = barometric pressure minus the vapor pressure of water at body temperature since alveolar gas is assumed to be water saturated, or 760 - 47 = 713 mm Hg. The slope or tan $\Theta$ of the body volume:mouth pressure is $\frac{\Delta V}{\Delta P}$ and $V_1$, or the thoracic gas volume ($V_{TG}$), is the volume of gas being compressed. $P_1$ is measured in mm Hg and must be multiplied by 1.36 to be converted to cm $H_2O$. The scale of the volume:pressure display are measured in millimeters and need to be converted to cm $H_2O$; Volume, 25 mm = 1 cm; Pressure, 5 mm = 1 cm; and the ratio of Volume:Pressure = 5. Hence,

$$V_1 + 713 \times 1.36 \times 5 \times \tan \Theta = 4848.40 \tan \Theta, \text{ and}$$

$$V_1 = V_{TG}$$

$$V_{TG} + IC = TLC$$

$$TLC - VC = RV,$$

where IC = inspiratory capacity, TLC = total lung capacity, VC = vital

capacity, and RV = residual volume. Body volume plethysmography was performed by Jim Virgulto, Electronics Engineer, Section of Pulmonary Medicine of the Yale University School of Medicine, and reviewed by Jacob Loke, M.D.

Data Analysis

Data were analyzed for statistical significance using Student's unpaired t-test except data for body fat content which was analyzed by Student's paired t-test. P values greater than 0.05 were considered to be not significant.

RESULTS

Part I: Thermoregulation during exercise in the heat

Esophageal ($T_{es}$) and mean skin ($\overline{T}_{sk}$) temperatures measured initially, at 1 minute pre-exercise, at threshold for vasodilation, and at the end of exercise are summarized in Table 3. The threshold for vasodilation was defined as the esophageal temperature at which forearm blood flow is 3 $ml \cdot min^{-1} \cdot 100\ ml^{-1}$; above this temperature, forearm blood flow (BF) rises linearly with $T_{es}$ (79). The differences between the means of $T_{es}$ and $\overline{T}_{sk}$ of the control and anorectic groups were not statistically significant ($P > 0.05$), but there was a tendency for the anorectic group to cluster at the higher end of the overlapping ranges. At the vasodilation $T_{es}$, the control group averaged 36.91°C, and the anorectic group averaged 37.34°C ($p = 0.05$). However the difference between the initial $T_{es}$ and the vasodilation threshold ($\Delta T$) was not statistically significant.

Figure 7 displays representative data (patient L.S.) of $T_{es}$, $\overline{T}_{sk}$ and BF relative to time in an ambient temperature ($T_a$) of 33°C. Over the course of exercise, there was a minimal rise (0.16°C) in $\overline{T}_{sk}$, the change in $T_{es}$ was 0.96°C, and the change in BF was 6.2 $ml \cdot min^{-1} \cdot 100\ ml^{-1}$. Blood flow remained low during rest and during the beginning of the exercise period. During exercise, the $T_{es}$ increased as warmed blood was transferred to the core from the exercising leg muscles. Meanwhile, mean forearm blood flow increased slowly until $T_{es}$ reached the vasodilation threshold; at this point, BF began to rise linearly with $T_{es}$ until it reached its near peak and began to plateau.

The relationship between forearm blood flow and esophageal

temperature is shown in Figure 8. Vasodilation threshold $T_{es}$ was determined as aforementioned, the BF:$T_{es}$ slope was determined by best-fit linear regression analysis; for each subject, all data points during exercise were averaged for mean $T_{es}$ ($\overline{T}_{es}$) and mean BF ($\overline{BF}$), and the steady state $\overline{T}_{es}$ and $\overline{BF}$ averaged data points collected during the last five minutes of exercise (Table 4). The mean of the slopes for the control group was 20.8, and was 13.2 for the anorectic group. The mean $\overline{T}_{es}$ for the control group was 37.40°C, and was 37.58°C for the anorectic group. The mean steady state $T_{es}$ was 37.67°C for the control group, and was 37.79°C for the anorectic patients. The differences between the means of the slopes, $\overline{T}_{es}$, and steady state $\overline{T}_{es}$ were not statistically significant, although there was a trend for $\overline{T}_{es}$ and steady state $\overline{T}_{es}$ to be higher in the anorectic group. Mean $\overline{BF}$ for the control group was 12.5 $ml \cdot min^{-1} \cdot 100\ ml^{-1}$, and was 6.0 $ml \cdot min^{-1} \cdot 100\ ml^{-1}$ for the anorectic group; this difference was statistically significant ($0.001 < p < 0.01$). Steady state BF for the control group was 15.1 $ml \cdot min^{-1} \cdot 100\ ml^{-1}$, 8.5 $ml \cdot min^{-1} \cdot 100\ ml^{-1}$ for the anorectic group, and the difference was also statistically significant ($0.01 < p < 0.02$).

Metabolic data are shown in Table 5; $\dot{V}O_2$ was corrected to STPD and normalized per kilogram body weight. Mean $\dot{V}O_2$ for the control group was 3.02 $ml \cdot min^{-1} \cdot kg^{-1}$ at rest and reached 22.62 $ml \cdot min^{-1} \cdot kg^{-1}$ at 15 minutes of exercise. Mean $\dot{V}O_2$ for the anorectic group was 3.16 $ml \cdot min^{-1} \cdot kg^{-1}$ at rest and reached 19.04 $ml \cdot min^{-1} \cdot kg^{-1}$ at 15 minutes of exercise; the differences between the patient and control groups were not statistically significant. Respiratory exchange ratios (R) between the two groups were not statistically significant.

The relationship bewteen $\dot{V}O_2$ and power during exercise is shown

in Table 6 and Figure 9. Force (kp) was converted to power (Watts) by the following equivalencies:

1 kilopound (kp) = 9.80665 $kg \cdot m \cdot sec^{-2}$, where 1 kp = force acting on 1 kg at gravity.

Work = Force x distance

$= kg \cdot m \cdot sec^{-2} \cdot m = kg \cdot m^{2} \cdot sec^{-2}$; and

Power = Work x $time^{-1}$

$= kg \cdot m^{2} \cdot sec^{-2} \cdot sec^{-1} = kg \cdot m^{2} \cdot sec^{-3}$.

Therefore, the power required to move a flywheel of 6 meters circumference from which a 1 kilogram mass is suspended at 60 revolutions per minute is:

Power = (9.80665 $kg \cdot m \cdot sec^{-2}$) (6 m) (60 $min^{-1}$) ($min \cdot 60\ sec^{-1}$)

$= 58.84\ kg \cdot m^{2} \cdot sec^{-3}$ = 58.84 Watts, where Watts are defined as $kg \cdot m^{2} \cdot sec^{-3}$. Data points were plotted and best-fit lines by regression analysis were drawn:

$\dot{V}O_2 = 0.23$ (x Watts) + 5.21, (r = 0.73) for the control group; and $\dot{V}O_2 = 0.24$ (x Watts) + 7.47, (r = 0.70) for the anorectic group. The regression lines are parallel and both groups have similar oxygen uptakes as a function of power; standard error bars around the means on the regression lines overlap ($\bar{x}$ = 22.8 $ml \cdot min^{-1} \cdot kg^{-1}$ ± 2.25, and 18.9 $ml \cdot min^{-1} \cdot kg^{-1}$ ± 2.25 for the control and anorectic groups, respectively).

Data from chemical analyses of blood samples obtained pre- and immediately post-exercise are presented in Table 7. Blood levels were within normal limits and remained essentially unchanged during the exercise period, except patient S.A. whose triglycerides were elevated to 306 mg% pre-exercise and 195 mg% post-exercise. It is interesting to also note that four of the five anorectic patients (all except L.E.)

had at least a two- to three-fold increase in lactic acid concentrations during exercise, whereas only one (D.C.) of four control subjects showed a similar increase. Determinations for lactic acid (control subject E.G.) and urea nitrogen (patient L.S.) were not obtained secondary to laboratory error.

Part II: Assessment of adipose stores by two methods

Data from the skinfold thickness and body density methods are shown in Table 8. The equations used in calculating the percent body fat are described in the Methods section. The mean percent body fat by the skinfold thickness method was 6.9%, whereas the body density measurement predicted the mean percent body fat as 11.8%. In three of the five anorectic patients (D.R., C.M., S.A.), there was a two-fold or greater percent body fat when predicted by the body density method, reaching statistical significance ($0.02 < p < 0.05$) using Student's paired t-test.

DISCUSSION

Part I: Thermoregulation during exercise in the heat

Blood flow to muscle increases during exercise in order to provide the oxygen and nutrients that are necessary to sustain exercise. The fuel energy is converted to mechanical work and thermal energy, heat. During the beginning of exercise, thermal energy is stored in the muscle; hence, the temperature of the muscle increases. Arterial blood is at core temperature as it enters the muscle; it thermally equilibrates with the muscles in the capillary beds, and venous blood leaves at muscle temperature. As a result of this heat transfer from working muscles to blood, the temperatures of the arterial blood and body (core) are increased.

When body core temperature increases, blood flow to the skin does likewise. The thermal energy produced in muscles during exercise is then transferred in the blood from core to skin, from where it can be dissipated to the environment by convection, radiation, and evaporation of sweat. Convection is the process by which the transfer of heat from the skin to the air is dependent on the temperature gradient and air velocity. Radiation is the transfer of heat by long wave electromagnetic emissions and is dependent on the temperature gradient between skin and body temperature. Conduction is dependent on direct contact between two surfaces and plays a negligible role in heat transfer. Evaporative sweat loss is dependent on the water vapor pressure gradient between the skin and the air. Thermal energy loss via the respiratory tract also plays a minor role, and is dependent on evaporation and convection. At low ambient temperature ($T_a$ 10$^{o}$C), convection

plays a major (> 50%) role in thermal energy exchange, whereas radiation and evaporative sweat loss each account for approximately 20% of the total heat loss. Respiratory loss acounts for approximately 10% of total heat loss. Heat loss by convection and radiation is potentially high since there is a large temperature gradient between the skin and the air. At high ambient temperatures, however, evaporative sweat loss plays the major role in total heat loss. The potential for heat loss by convection, radiation, and respiration decreases as the skin temperature rises with ambient temperature (53). In the thermal steady state, when mean core temperature is constant, this may be summarized in the following energy balance equation, expressed in $Watts \cdot m^{-2}$:

$$M = E \pm (R + C) + (\pm W),$$

where M = rate of energy metabolism

E = rate of evaporative loss

R + C = rate of radiant and convective loss, when the sign is positive

W = work rate, where +W is work done on an external system and -W is work absorbed by the body.

If there is a thermal unsteady state with a subsequent change in core temperature, a heat storage term (S) must be added:

$$S = M = E \pm (R + C) - (\pm W),$$

where +S represents an increase in core temperature (57).

Esophageal ($T_{es}$) and mean skin ($\overline{T}_{sk}$) temperatures in the control and anorectic subjects did not differ significantly except at the vasodilation threshold $T_{es}$ where the anorectic group mean temperature was $0.43^{o}C$ greater than the control group mean temperature (Table 3).

This finding of an elevated $T_{es}$ threshold for cutaneous vasodilation markedly contrasts the results of Luck and Wakeling (47), who found that anorectic subjects demonstrated a "shift to the left" and vasodilated at lower core and mean skin temperatures than control subjects. It seems unlikely that anorectic patients would have lowered thresholds for vasodilation and thermoregulatory sweating; anorectic patients are observed to dress in layers of clothing, are maximally vasoconstricted in an ambient temperature of 28°C, have decreased fat insulation (2,40), note feeling cold even during the summer, and rarely sweat even during exercise in the heat.

The paradoxical effect noted by Luck and Wakeling (47) may merely reflect their experimental design; in an ambient temperature of 20°C, lightly clad subjects rested 30 minutes prior to immersion to calf-level in water heated to 42°C. "Core" temperature, measured with a sublingual thermistor, was significantly lower (1°C) in the anorectic group initially and was attributed to low metabolic rates and lowered thresholds for thermoregulatory sweating and vasodilation. Although Luck and Wakeling found no significant differences between rectal and oral (sublingual) temperatures in a preliminary study, it is not generally accepted that oral (sublingual) temperature is an adequate reflection of core temperature because of the relatively great time delay in response to a change in thermal load. There has been controversy over the optimal site--rectal, esophageal, tympanic membrane--for measuring core temperature, but evidence supports esophageal temperature as being the best index of the temperatures of the deep thermoreceptors important in thermoregulation (62). Furthermore, Jéquier (40) has shown that in an ambient temperature of 20°C, anorectic patients produce less heat

than they lose, and their metabolic heat production is significantly ($p < 0.01$) less, even though their heat losses are similar when compared to control subjects. Hence, it is reasonable that Luck and Wakeling found the initial mean temperature in the anorectic patients to be $1^{\circ}C$ lower (range $34.4^{\circ}$ to $35.9^{\circ}C$) than the controls; in a cool environment, the anorectic patients are at increased risk for hypothermia. The explanation that in cooler ambient temperatures, low core temperature might reflect metabolic heat production which is less than heat losses in anorectic patients is supported indirectly by this data (normal core temperature at $T_a$ $33^{\circ}C$), by Luck and Wakeling (normal core temperature at $T_a$ $30^{\circ}C$) (48), by Mecklenburg (low core temperature at $T_a$ $10^{\circ}C$) (50), and by Davies, Fohlin and Thorén (21). Davies, et al. studied the effects of "preheating" anorectic patients in a sauna prior to exercise and found that the resting rectal temperature was increased, but the rate of change and the final "plateau" temperature were both virtually unchanged.

Mean forearm blood flow ($\overline{BF}$) and steady state $\overline{BF}$ exhibited statistically significant differences approximating two-fold ($0.001 < p < 0.01$ and $0.01 < p < 0.02$, respectively) between the control and anorectic groups (Figure 8, Table 4). This contradicts the findings of Luck and Wakeling (47) in which maximal blood flow was greater in the anorectic patients and extended over a wider range; this could reflect their patient population, since it is generally accepted that patients with anorexia nervosa are relatively vasoconstricted even with thermal stress (25,28,50,74). The relationship between BF and $T_{es}$, i.e., slope, was similar in both groups. Anorectic patients vasodilated with a normal response to an increase in core temperature, yet they "reset"

their vasodilation threshold $T_{es}$ to a higher level, and BF plateaued at a lower level. Hence, it is concluded that patients with anorexia nervosa thermoregulate, and the sensitivity of the peripheral thermoregulatory sensors is unchanged. This conclusion is consistent with data from Davies, et al. (21), and Wakeling and Russell (74), although the "sluggish" response reported by the latter group of investigators was not supported.

The thermoregulatory responses of the anorectic patients are similar to those of subjects rendered hypovolemic during exercise for 30 minutes at $\dot{V}O_2$ max in an ambient temperature of 35°C. The mean vasodilation threshold $T_{es}$ was 36.90°C in normovolemic experiments and 37.32°C in the hypovolemic experiments; the upward shift in the threshold is believed to be mediated by low pressure baroreceptors. In addition, maximal blood flow was decreased in the hypovolemic experiments and was attributed to a progressive fall in cardiac stroke volume (59). The means and amount of shift in the vasodilation threshold $T_{es}$ are identical between the anorectic and control groups, and between the normovolemic and hypovolemic experiments; vasodilation threshold $T_{es}$ for controls was 36.91°C and 37.34°C for anorectic patients (Figure 10). Blood volume determinations by the Evan's blue dye dilution method were not done in the present study, secondary to the patients' reluctance to have additional blood samples drawn. The one-step rebreathing technique for estimating cardiac output requires extensive training, hence it was not done in the present study (2,58). Clinical assessment, however, did not reveal the signs of moderate to severe dehydration in the anorectic patients that would have accompanied an 11% reduction in blood volume as achieved by the subjects rendered

hypovolemic with diuretics. It is unlikely that the anorectic patients were hypovolemic; routine screening tests did not reveal electrolyte imbalances, increased hematocrits, nor evidence of partial diabetes insipidus as suggested by Mecklenburg (50). In fact, anorectic patients may exhibit polydipsia in an attempt to increase weight gain without increasing caloric intake.

Evaporative sweat loss was measured by absolute weight loss (in grams) and found to be significantly less ($0.02 < p < 0.05$) in the anorectic group ($x \pm SD = 246.6 \pm 102.25$; range 123 to 405) compared to the control group 406 ± 93.1; range 309 to 507). When sweat loss was normalized for body surface area ($grams \cdot m^{-2}$), however, the differences were not statistically significant between the anorectic group ($x \pm SD = 174.6 \pm 67.4$; range 91.8 to 279.3) and the control group (255.7 ± 52.4; range 195.6 to 312.9). This contradicts anecdotes that anorectics do not thermoregulate by sweating. Evaporative sweat loss in this investigation cannot be expressed in Watts, nor can conclusions about energy balance be drawn, since the total length of time in the climate-controlled chamber varied. Variable factors included preparatory and recovery times. Davies, et al. (21) reported that absolute evaporative sweat loss was lower in anorectics and in control subjects, and in relation to total heat production, their evaporative sweat loss lay within the lower limits of normal.

Resting metabolic rate in anorectics was not lower than controls (Table 5). In addition, there was no evidence of a bradycardia at rest, contrary to descriptions by other investigators (2,25,67). This latter finding may reflect the increase in cardiac output needed in the heat for temperature regulation, especially in unacclimatized individ-

uals (69). Fohlin, et al. (26) reported a mean $\dot{V}O_2$ (corrected to STPD) at rest of 0.139 $l \cdot min^{-1}$ for 17 female patients with anorexia nervosa, a $\dot{V}O_2$ that was approximately 20% lower than expected; control subjects were not studied, but data from trained, physically fit children were used for comparison. Mean $\dot{V}O_2$ (corrected to STPD) at rest was 0.131 $l \cdot min^{-1} \pm 0.016$ for the anorectic patients and was 0.173 $l \cdot min^{-1} \pm 0.009$ for the control subjects in the present study. There was also an approximately 20% difference ($0.02 < p < 0.05$) between the two groups; however, making such a comparison is erroneous since the oxygen uptake has not been normalized for body weight. Normalization of oxygen uptake permits comparisons of metabolic rates which are independent of body size between different individuals. When this normalization has been made, the metabolic rates are similar (Table 5). The average percent weight loss in Fohlin's group of anorectic patients was approximately 25% and could account for the 20% decrease in resting $\dot{V}O_2$ ($l \cdot min^{-1}$).

The differences between the means of the respiratory exchange ratios (R) of the two groups (Table 5) were not statistically significant; however, there was a tendency for greater R values in the anorectic patients than in the control subjects. At 15 minutes of exercise, the range of R values for the anorectic patients was between 0.81 and 1.21, whereas the range for the control subjects was between 0.81 and 0.96. The R value obtained from oxidizing a pure carbohydrate is 1.00, is 0.70 from fat oxidation, and is 0.83 from catabolism of meat protein (44,64). R values greater than 1.00 reflect an increase in the rate of $CO_2$ elimination, not necessarily $CO_2$ produced from oxidation, but from, for example, hyperventilation as a consequence of formation

of acids such as lactic acid or keto-acids, as well as acid retention seen in nephritis and uremia, and "laying down of fat at the expense of carbohydrate". Increases in $CO_2$ production are seen with oxidation of pyruvic and glycuronic acids, each yielding an R value of 1.2 (64).

The anorectic patients were in the recovery phase at the time of the study; they had gained insight in their disorder and were recovering their lost weight. Hence, the synthesis of fat from carbohydrate certainly could have altered the R value by increasing it. However, this effect would have a greater influence at rest than during exercise when increased energy demands would decrease fat synthesis. It is unlikely that the R value elevations in the anorectic patients were secondary to acid retention; they had no history of renal disease. Nor is it likely that pyruvic or glycuronic acids were their main sources of fuel.

The most likely explanation for the elevated R values in the anorectic patients is the combination of hyperventilation and formation of lactic acid (Table 7). In four of the five patients (all except L.E.), there was at least a two- to three-fold increase in lactic acid concentration during exercise; these were only slightly elevated over the normal resting range of 6 to 16 mg%. At $\dot{V}O_2$ max, the blood lactic acid concentrations can be above 70 to 80 mg% (4). When the ratio of the expiratory gas volume$\cdot$min$^{-1}$ ($\dot{V}_E$) to oxygen uptake$\cdot$min$^{-1}$ ($\dot{V}O_2$) is greater than 23 liters$\cdot$liter$^{-1}$, a subject is, by definition, hyperventilating (4). Hyperventilation occurs when the work load cannot be sustained entirely aerobically. In the control subjects, the mean $\dot{V}_E$:$\dot{V}O_2$ ratio was 27.25 liters$\cdot$liter$^{-1}$ $\pm$ 1.77, and was 29.90 liters$\cdot$liter$^{-1}$ $\pm$ 2.17 in the anorectic patients; by definition, both groups

were hyperventilating. Although the difference between the means of the ratios was not statistically significant, the range for the anorectic patients (23.25 to 34.80) tended to be greater than for the control subjects (23.15 to 31.83).

There is some controversy concerning the mechanism(s) stimulating the hyperventilation; the effect of lactic acid on blood pH, hypoxia and variations in $P_{O_2}$ and $P_{CO_2}$ on central and peripheral chemoreceptors, and neurogenic factors have been studied (4). The possibility thence arises that the anorectic patients were working at a greater percent $\dot{V}O_2$ max than the control subjects; if so, the original premise that the work load and percent $\dot{V}O_2$ max could be estimated from the heart rate response (4) may have been incorrect in the anorectic patients. Another possibility is that the anorectic patients may not have been as able to meet the demands for increased cardiac output while exercising in the heat since blood flow to muscle and skin needed to be increased. It has been suggested that the reduction in maximal forearm blood flow seen in hypovolemic subjects may be secondary to a progressive fall in cardiac stroke volume and the low pressure baroreceptors mediated an increase in the vasodilation threshold $T_{es}$ (59). Perhaps such factors affected not only the vasodilation threshold $T_{es}$ and maximal forearm blood flow, but may have mediated or altered the threshold of the ventilatory drive mechanism(s) in anorectic patients.

During exercise, the oxygen uptake for a given level of exercise power was similar in both the control and anorectic groups (Table 6, Figure 9); the regression lines were parallel and essentially nondisplaced when standard error bars were drawn. Direct comparisons between the two groups could not be made, however, since the anorectic subjects

tended to cluster at the lower levels of power output, most likely secondary to their small muscle mass. Fohlin, et al. (26) reported that the regression line describing the anorectic patients was displaced parallel to and below the "normal", i.e., trained, physically fit children. The authors suggested that children with anorexia nervosa might pedal with greater mechanical efficiency, but also noted that the regression line was equally displaced at rest. Fohlin, et al. again neglected to correct oxygen uptake for body weight; if they had done so, they would have found the relationship between $\dot{V}O_2$ and power to be similar in both groups as found in this study, and they could not have suggested the possibility of greater mechanical efficiency in the anorectic group.

Part II: Assessment of adipose stores by two methods

Jackson (39) reported that assessment of adipose stores from skinfold thickness measurements are population-specific, particularly for age and body composition. The largest single depot of adipose tissue is believed to be subcutaneous, probably accounting for at least 50% of the total adipose tissue; other large depots include intra-abdominal, intra- and intermuscular. The thickness of subcutaneous fat differs according to region and individual (43).

During starvation, body fat stores are lost before protein (skeletal muscle) is catabolized. Bone, kidney, stomach, small intestine, and brain are relatively spared compared to fat and skeletal muscle. In addition, mammary glands tend to be spared during starvation and a "remarkable preservation of breasts in some cases with anorexia nervosa" has been noted (43).

Keys and Brozek, et al. (43) cited a study in which concentration camp victims were re-fed and were noted to replace fat before muscle mass, so that they reached greater than pre-starvation levels; a decrease in fat was noted after 33 weeks post-semistarvation, and fat returned to normal levels at 58 weeks post-semistarvation.

The mean percent body fat for five anorectic patients was 6.9% by the skinfold thickness method. The body density determination predicted the mean percent body fat to be 11.8%. The difference between these two means was statistically significant ($0.02 < p < 0.05$), and could be attributed to inherent errors in both methods for predicting percent body fat.

The skinfold thickness method does not account for the "deeper" fat deposits, nor does it measure the fat amassed in breast tissue or in the gluteal region. Hence, this method could underestimate the percent body fat. However, comparisons between this method and body density measurements in athletes of both sexes over time yielded a correlation coefficient of 0.9762 and a standard error of the estimate as 1.06% (2). Variations in measurements are generally avoided by having a single, experienced observer make the measurements.

Higher percent body fat by the body density method may have been predicted secondary to buoyancy of adipose tissue from the breasts, gluteal region, and intra-abdominal tissues, and from the gas volume present in the gastrointestinal tract. The volume of urine and feces can also affect buoyancy. The effect of the gas volume in the gastrointestinal tract and the volume of urine and feces were minimized by making the measurements during the post-absorptive state and after the patients voided.

The patients were submerged in the supine position; there is the possibility that maximal expiration could not be achieved in this position. If so, estimation of a greater percent body fat than exists would reflect the increased buoyancy of the retained gas in the lungs. Another possibility is that skeletal muscle was not fully replaced in the anorectic patients. During starvation, the percent dry matter in skeletal muscle is decreased; hence, muscle is relatively "waterlogged" (43). This would decrease the specific gravity and increase the predicted percent body fat. This must be considered in the anorectic patients since they were in the recovery phase during this study.

Other body composition factors which could have affected the body density determinations include state of hydration, and any changes in the relative mass of bone. The anorectic patients were clinically euvolemic. Klibanski, et al. (45) reported decreased bone density in women with hyperprolactinemic amenorrhea, but found no significant correlation between serum prolactin concentration and bone density ($r = -0.27$). However, they did find that patients with undetectable serum estradiol concentrations ($< 20$ pg/ml) had significantly lower bone densities compared to age-matched controls ($p < 0.001$) and to patients with higher ($> 20$ pg/ml) serum estradiol concentrations ($p < 0.01$). Cann (15) reported that women with amenorrhea secondary to exercise were at risk for developing early osteoporosis, possibly due to decreased body fat and its associated decrease in estrone and estradiol levels. Patients with anorexia nervosa have normal serum prolactin and lower serum estradiol and estrone concentrations (2). A decrease in bone density could result in anorectic patients with amenorrhea (such as those in this study) secondary to decreased body

fat and low estrogen levels. A decrease in bone density would increase the predicted percent body fat than exists.

Conclusions concerning the validity of either method in the assessment of adipose stores in anorectic patients cannot be made from this study; the sample size is inadequate. It is interesting to note, however, that a similar discrepancy was encountered in measurements of female gymnasts, but not in other athletes (3). The skinfold thickness method is recommended for the assessment of adipose stores in patients with anorexia nervosa, keeping in mind that this may underestimate the percent body fat since the "deeper" fat deposits, fat amassed in breast tissue or in the gluteal region are not measured. The body density method may be less accurate because of the gas volume present in the gastrointestinal tract, volume of urine and feces, and the changes in muscle and bone mass associated with starvation. In addition, the ease of performing the skinfold thickness method makes it attractive for assessing adipose stores.

REFERENCES


1. American Psychiatric Association: Diagnostic and Statistical Manual of Nervous Disorders, Third Edition: DSM-III. Washington, D.C., APA, 1980.

2. Anyan, W.R.: Adolescent Medicine in Primary Care. New York, John Wiley & Sons, 1978.

3. Anyan, W.R.: personal communication.

4. Åstrand, P.O. and K. Rodahl: Textbook of Work Physiology: Physiological Bases of Exercise, 2nd Edition. New York, McGraw-Hill Book Company, 1977.

5. Berkman, J.M.: Anorexia nervosa, anorexia, inanition, and low basal metabolic rate. Am. J. Med. Sci. 180:411-424, 1930.

6. Bigland-Ritchie, B., H. Graichen and J.J. Woods: A variable-speed motorized bicycle ergometer for positive and negative work exercise. J. Appl. Physiol. 35:739-740, 1973.

7. Boyar, R.M.: Reply to the editor. N. Engl. J. Med. 296:1069, 1977.

8. Boyar, R.M., L.D. Hellman, H. Roffwarg, J. Katz, B. Zumoff, J. O'Connor, H.L. Bradlow and D.K. Fukushima: Cortisol secretion and metabolism in anorexia nervosa. N. Engl. J. Med. 296:190-193, 1977.

9. Boyar, R.M., J. Katz, J.W. Finkelstein, S. Kapen, H. Weiner, E.D. Weitzman and L. Hellman: Anorexia nervosa: immaturity of the 24-hour luteinizing hormone secretory pattern. N. Engl. J. Med. 291:861-865, 1974.

10. Bruch, H.: Eating Disorders: Obesity and Anorexia Nervosa. New York, Basic Books, 1973.

11. Bruch, H.: Perceptual and conceptual disturbances in anorexia nervosa. Psychosom. Med. 24:187-194, 1962.

12. Bruch, H.: The psychiatric differential diagnosis of anorexia nervosa. In: Anorexia Nervosa: Symposium a.m. 24/25 April 1965 in Gottingen Meyer, J.E., and Feldman, H., eds., Stuttgart, Georg Thieme, 1965, pp. 70-86.

13. Bruch, H.: Psychotherapy in primary anorexia nervosa. J. Nerv. Ment. Dis. 150:52-67, 1970.

14. Burman, K.D., R.A. Vigersky, D.L. Loriaux, D. Strum, Y.Y. Djuh, F.D. Wright and L. Wartofsky: Investigations concerning thyroxine deiodinative pathways in patients with anorexia nervosa. In: Anorexia Nervosa, Vigersky, R.A., ed., New York, Raven Press, 1977,

pp. 255-261.

15. Cann, C.E., cited by: Gonzalez, E.R.: Premature bone loss found in some nonmenstruating sportswomen. JAMA 248:513-514, 1982.

16. Carpenter, T.M.: Tables, Factors, and Formulas for Computing Respiratory Exchange and Biological Transformations of Energy. Washington, D.C., Carnegie Institution of Washington, 1921.

17. Casper, R.C., R.T. Chatterton, Jr. and J.M. Davis: Alterations in serum cortisol and its binding characteristics in anorexia nervosa. J. Clin. Endocrinol. Metab. 49:406-411.

18. Cecil's Textbook of Medicine, 5th Edition. Cecil, R.L., ed. Philadelphia, W.B. Saunders Company, 1940, pp. 744-745.

19. Chopra, I.J., U. Chopra, S.R. Smith, M. Raza and P.H. Solomon: Reciprocal changes in serum concentration of 3, 3', 5' $T_3$ (reverse $T_3$) and 3, 3', 5 $T_3$ ($T_3$) in systemic illness. J. Clin. Endocrinol. Metab. 41:1043-1049, 1975.

20. Crisp, A.H.: Clinical and therapeutic aspects of anorexia nervosa: a study of 30 cases. J. Psychosom. Res. 9:67-78, 1965.

21. Davies, C.T.M., L. Fohlin and C. Thorén: Temperature regulation in anorexia nervosa patients during prolonged exercise. Acta. Med. Scand. 205:257-262, 1979.

22. Farhi, L.E., M.S. Nesarajah, A.J. Olszowka, L.A. Metildi and A.K. Ellis: Cardiac output determination by simple one-step rebreathing technique. Respir. Physiol. 28:141-159, 1976.

23. Feicht, C.B., T.S. Johnson, B.J. Martin, K.E. Sparkes and W.W. Wagner, Jr.: Secondary amenorrhea in athletes. Lancet 2:1145-1146, 1978.

24. Feighner, J.P., E. Robins, S.B. Guze, R.A. Woodruff, Jr., G. Winokur and R. Munoz: Diagnostic criteria for use in psychiatric research. Arch. Gen. Psychiatry 26:57-63, 1972.

25. Fohlin, L.: Body composition, cardiovascular and renal function in adolescent patients with anorexia nervosa. Acta. Paediatr. Scand. Suppl 268:1-20, 1977.

26. Fohlin, L., U. Freyschuss, B. Bjarke, C.T.M. Davies and C. Thorén: Function and dimensions of the circulatory system in anorexia nervosa. Acta. Paediatr. Scand. 67:11-16, 1978.

27. Forbes, G.B.: Relation of lean body mass to height in children and adolescents. Pediat. Res. 6:32-37, 1972.

28. Freyschuss, U., L. Fohlin and C. Thorén: Limb circulation in anorexia nervosa. Acta. Paediatr. Scand. 67:225-228, 1978.

29. Frisch, R.E., A.V. Got-Welbergen, J.W. McArthur, T. Albright, J. Witschi, B. Bullen, J. Bimloz, R.B. Read and H. Hermann: Delayed menarche and amenorrhea of college athletes in relation to age of onset of training. JAMA 246:1559-1563, 1981.

30. Frisch, R.E. and J.W. McArthur: Menstrual Cycles: fatness as a determinant of minimum weight for height necessary for their maintenance or onset. Science 185:949-951, 1974.

31. Frisch, R.E. and R. Revelle: Height and weight at menarche and a hypothesis of menarche. Arch. Dis. Child. 46:695-701, 1971.

32. Frisch, R.E. and R. Revelle: Variation in body weights and the age of the adolescent growth spurt among Latin American and Asian populations in relation to caloric supplies. Human Biol. 41:185-212, 1969.

33. Frisch, R.E., G. Wyshak and L. Vincent: Delayed menarche and amenorrhea in ballet dancers. N. Engl. J. Med. 303:17-19, 1980.

34. Gull, W.W.: Address in medicine. Lancet 2:171-176, 1868.

35. Gull, W.W.: Anorexia hysterica (apepsia hysterica). Br. Med. J. 2:527-528, 1873.

36. Gull, W.W.: Anorexia nervosa (apepsia hysterica, anorexia hysterica). Trans. Clin. Soc. London 7:22-28, 1874.

37. Gull, W.W.: Anorexia nervosa. Lancet 1:516-517, 1888.

38. Halmi, K.A., P. Powers and S. Cunningham: Treatment of anorexia nervosa with behavior modification: effectiveness of formula feeding and isolation. Arch. Gen. Psychiatry 32:93-96, 1975.

39. Jackson, A.S., M.L. Pollock and A. Ward: Generalized equations for predicting body density of women. Med. Sci. Sports Exercise. 12:175-182, 1980.

40. Jequier, E.: Human energy needs and expenditure: Relationship to the regulation of energy balance. Z. Ernährungswiss Suppl 23:1-9, 1979.

41. Kalucy, R.S., A.H. Crisp and B. Harding: A study of 56 families with anorexia nervosa. Br. J. Psychol. 50:381-395, 1977.

42. Keys, A. and J. Brozek: Body fat in adult man. Physiol. Rev. 33:245-325, 1953.

43. Keys, A., J. Brozek, A. Henschel, O. Mickelson and H.L. Taylor: The Biology of Human Starvation. Minneapolis, University of Minnesota Press, 1950

44. Kleiber, M.: The Fire of Life: an introduction to animal energet-

ics. New York, Robert E. Kreiger Publishing Company, 1975.

45. Klibanski, A., R.M. Neer, I.Z. Beitins, E.C. Ridgeway, N.T. Zervas and J.W. McArthur: Decreased bone density in hyperprolactinemic women. N. Engl. J. Med. 303:1511-1514, 1980.

46. Lucas, A.: Toward the understanding of anorexia nervosa as a disease entity. Mayo Clin. Proc. 56:254-264, 1981.

47. Luck, P. and A. Wakeling: Altered thresholds for thermoregulatory sweating and vasodilation in anorexia nervosa. Br. Med. J. 281: 906-908, 1980.

48. Luck, P. and A. Wakeling: Increased cutaneous vasoreactivity to cold in anorexia nervosa. Clin. Sci. 61:559-567, 1981.

49. Marshall, J.C. and T.R. Fraser: Amenorrhea in anorexia nervosa: assessment and treatment with clomiphene citrate. Br. Med. J. 4:590-592, 1971.

50. Mecklenburg, R.S., D.L. Loriaux, R.H. Thompson, A.E. Andersen and M.B. Lipsett: Hypothalamic dysfunction in patients with anorexia nervosa. Medicine (Baltimore). 53:147-159, 1974.

51. Miller, M., T. Dalakos, A.M. Moses, H. Fellerman and D.H.P. Streeten: Recognition of partial defects in antidiuretic hormone secretion. Ann. Intern. Med. 73:721-729, 1970.

52. Minuchin, S., B.L. Rosman and L. Baker: Psychosomatic Families: Anorexia Nervosa in Context. Cambridge, Harvard University Press, 1978.

53. Mitchell, J.W.: Energy exchanges during exercise. In: Problems with Temperature Regulation During Exercise, Nadel, E.R., ed., New York, Academic Press, 1977, pp. 11-26.

54. Miyai, K., T. Yamamoto, M. Azukizawa, K. Ishibashi and Y. Kumahara: Serum thyroid hormones and thyrotropin in anorexia nervosa. J. Clin. Endocrinol. Metab. 40:334-338, 1975.

55. Moshang, T., Jr., J.S. Parks, L. Baker, V. Vaidya, R.D. Utiger, A.M. Bongiovanni and P.J. Snyder: Low serum triiodothyronine in patients with anorexia nervosa. J. Clin. Endocrinol. Metab. 40:470-473, 1975.

56. Moshang, T., Jr. and R.D. Utiger: Low triiodothyronine euthyroidism in anorexia nervosa. In: Anorexia Nervosa, Vigersky, R.A., ed., New York, Raven Press, 1977, pp. 263-270.

57. Nadel, E.R.: Temperature regulation. In: Sports Medicine and Physiology, Strauss, R.H., ed., Philadelphia, W.B. Saunders Co., 1979, pp. 130-146.

58. Nadel, E.R., E. Cafarelli, M.F. Roberts and C.B. Wenger: Circulatory regulation during exercise in different ambient temperatures. J. Appl. Physiol. 46:430-437, 1979.

59. Nadel, E.R., S. Fortney and C.B. Wenger: Effect of hydration state on circulatory and thermal regulations. J. Appl. Physiol. 49:715-721, 1980.

60. Osler's Principles and Practice of Medicine, 13th Edition. Revised by Christian, H.A. and T. McCrae, New York, D. Appleton-Century Co., 1938, pp. 1136-1137.

61. Palazzoli, S.M.: Self starvation: from Individual to Family Therapy in the Treatment of Anorexia Nervosa. New York, Jason Aronson, 1978.

62. Phronen, P.: Sinusoidal signals in the analysis of heat transfer in the body. In: Physiological and Behavioral Temperature Regulation. Hardy, J.D., A.P. Gagge and J.A.J. Stolwijk, eds., Springfield, Charles C. Thomas, 1970.

63. Ricci, B.: Experiments in the Physiology of Human Performance. Philadelphia, Lea and Febiger, 1970, pp. 27-34, 184.

64. Richardson, H.B.: The respiratory quotient. Physiol. Rev. 9:61-125, 1929.

65. Roddie, I.C., J.T. Shepherd and R.F. Whelan: Evidence from venous oxygen saturation measurements that the increase in forearm blood flow during body heating is confined to the skin. J. Physiol. (London) 134:444-450, 1956.

66. Schmidt-Nielsen, K.: Animal Physiology: Adaptation and Environment. London, Cambridge University Press, 1975, pp. 316-331.

67. Schwabe, A.D., B.M. Lippe, J. Chang, M.A. Pops and J. Yager: UCLA Conference: Anorexia nervosa. Ann. Intern. Med. 94:371-381.

68. Sherman, B.M., K.A. Halmi and R. Zamudio: LH and FSH response to gonadotropin-releasing hormone in anorexia nervosa: effect of nutritional rehabilitation. J. Clin. Endocrinol. Metab. 41:135-142, 1975.

69. Stolwijk, J.A.J., M.F. Roberts, C.B. Wenger and E.R. Nadel: Changes in thermoregulatory and cardiovascular functions with heat acclimatization. In: Problems with Temperature Regulation during Exercise, Nadel, E.R., ed., New York, Academic Press, 1977, pp. 77-90.

70. Stonehill, E. and H. Nunnerley: Skin thickness and skinfold thickness in anorexia nervosa. Br. J. Derm. 85:158-161, 1971.

71. Vagenakis, A.G.: Thyroid hormone metabolism in prolonged experi-

mental starvation in man. In: Anorexia Nervosa, Vigersky, R.A., ed., New York, Raven Press, 1977, pp. 243-251.

72. Vigersky, R.A., A.E. Andersen, R.H. Thompson and D.L. Loriaux: Hypothalamic dysfunction in secondary amenorrhea associated with simple weight loss. N. Engl. J. Med. 297:1141-1145, 1977.

73. Vigersky, R.A., D.L. Loriaux, A.E. Andersen, R.S. Mecklenburg and J.L. Vaitukaitis: Delayed pituitary hormone response to LRF and TRF in patients with anorexia nervosa and with secondary amenorrhea associated with simple weight loss. J. Clin. Endocrinol. Metab. 43:893-900, 1976.

74. Wakeling, A. and G.F.M. Russell: Disturbances in the regulation of body temperature in anorexia nervosa. Psychol. Med. 1:30-39, 1970.

75. Waller, J.V., R.M. Kaufman and F. Deutsch: Anorexia nervosa: A psychosomatic entity. Psychosom. Med. 2:3-16, 1940.

76. Warren, M.P.: The effects of exercise on pubertal progression and reproductive function in girls. J. Clin. Endocrinol. Metab. 51:1150-1157, 1980.

77. Warren, M.P. and R.L. VandeWiele: Clinical and metabolic features of anorexia nervosa. Am. J. Obstet. Gynecol. 117:435-449, 1973.

78. Wenger, C.B. and M.F. Roberts: Control of forearm venous volume during exercise and body heating. J. Appl. Physiol. 48:114-119, 1980.

79. Wenger, C.B., M.F. Roberts, J.A.J. Stolwijk and E.R. Nadel: Forearm blood flow during body temperature transients produced by leg exercise. J. Appl. Physiol. 38:58-63, 1975.

80. Whitney, R.J.: The measurement of volume changes in human limbs. J. Physiol. (London) 121:1-27, 1953.

81. Winokur, A., V. March and J. Mendels: Primary affective disorders in relatives of patients with anorexia nervosa. Am. J. Psych. 137:695-698, 1980.

TABLE 2. Physical characteristics of subjects

| | Age (yr)[3] | Height (cm)[3] | Weight (kg)[4] | LBM (kg)[1] | Weight Score[2,5] |
|---|---|---|---|---|---|
| Controls (n=5) | | | | | |
| D.C. | 15 7/12 | 167.5 | 57.45 | 44.91 | 128 |
| C.Mc. | 23 8/12 | 165.6 | 56.78 | 43.37 | 131 |
| E.G. | 16 3/12 | 157.5 | 62.60 | 37.36 | 168 |
| D.M. | 15 10/12 | 159.4 | 56.74 | 38.69 | 147 |
| S.D. | 29 3/12 | 155.0 | 47.94 | 35.68 | 134 |
| Mean ± | 20 1/12 | 161.0 | 56.30 | | 142 |
| SD | 6 1/12 | 5.3 | 5.28 | | 16 |
| Anorectics (n=5) | | | | | |
| L.E. | 16 4/12 | 164.5 | 44.80 | 42.50 | 105 |
| D.R. | 18 1/12 | 161.3 | 42.71 | 40.07 | 107 |
| C.M. | 20 7/12 | 162.5 | 37.22 | 40.96 | 91 |
| S.A. | 15 7/12 | 159.4 | 38.60 | 38.69 | 100 |
| L.S. | 19 7/12 | 162.6 | 44.67 | 41.04 | 109 |
| Mean ± | 18 0/12 | 162.1 | 41.60 | | 102 |
| SD | 2 1/12 | 1.9 | 3.50 | | 7.2 |

[1] $LBM = 2.06e^{0.184\ ht}$, where LBM = lean body mass in kg, and ht = height in cm (27).

[2] Weight score = $\frac{BW \times 100}{\text{expected LBM}}$, where BW = body weight in kg, and LBM = lean body mass in kg (2).

[3] Not statistically significant, $p > 0.05$.

[4] $p < 0.001$

[5] $0.001 < p < 0.01$

TABLE 3. Summary of thermal data of control and anorectic subjects

| | Controls (n=5) Mean ± SE | Range | Anorectics (n=5) Mean ± SE | Range | p values for differences between means |
|---|---|---|---|---|---|
| Initial Temperature ($^{o}$C) | | | | | |
| Esophageal | 36.51± 0.23 | 35.81-37.04 | 36.93± 0.03 | 36.87-37.05 | N.S. |
| Mean Skin | 34.52± 0.42 | 33.05-35.68 | 35.06± 0.18 | 34.57-35.61 | N.S. |
| Temp ($^{o}$C) 1 min pre-exercise | | | | | |
| Esophageal | 36.94± 0.15 | 36.53-37.33 | 37.17± 0.08 | 36.93-37.41 | N.S. |
| Mean Skin | 34.66± 0.24 | 34.16-35.56 | 35.23± 0.24 | 34.40-35.72 | N.S. |
| Vasodilation threshold temp ($^{o}$C) | | | | | |
| Esophageal | 36.91± 0.17 | 36.36-37.30 | 37.34± 0.08 | 37.16-37.64 | 0.05 |
| Mean Skin | 34.67± 0.22 | 34.17-35.47 | 35.18± 0.17 | 34.83-35.71 | N.S. |
| Temp ($^{o}$C) end of exercise | | | | | |
| Esophageal | 37.72± 0.15 | 37.42-38.14 | 37.86± 0.06 | 37.69-38.03 | N.S. |
| Mean Skin | 34.65± 0.39 | 33.47-35.55 | 35.40± 0.18 | 34.84-35.87 | N.S. |
| Threshold Tes - Initial Tes ($\Delta$T) ($^{o}$C) | 0.40± 0.33 | | 0.41± 0.07 | | N.S. |

$p > 0.05$ N.S.

TABLE 4. Thermal and circulatory data of control and anorectic subjects during exercise

| | | | Mean | | Steady State | |
|---|---|---|---|---|---|---|
| Controls (n=5) | Threshold Tes (°C) | Slope | Tes (°C) | BF ($ml \cdot min^{-1} \cdot 100ml^{-1}$) | Tes (°C) | BF ($ml \cdot min^{-1} \cdot 100ml^{-1}$) |
| D.C. | 37.14 | 10.098 | 37.76 | 9.25 | 38.13 | 10.41 |
| C.Mc. | 36.74 | 22.161 | 37.09 | 10.94 | 37.37 | 13.20 |
| E.G. | 37.30 | 17.917 | 37.73 | 10.67 | 37.94 | 14.01 |
| D.M. | 37.02 | 30.591 | 37.32 | 12.04 | 37.40 | 14.08 |
| S.D. | 36.36 | 23.221 | 37.09 | 19.81 | 37.50 | 23.83 |
| Mean ± | 36.91 | 20.798 | 37.40 | 12.54 | 37.67 | 15.11 |
| SE | 0.17 | 3.365 | 0.15 | 1.87 | 0.16 | 2.28 |
| Anorectics (n=5) | | | | | | |
| L.E. | 37.39 | 9.342 | 37.76 | 6.39 | 38.00 | 8.83 |
| D.R. | 37.20 | 12.497 | 37.48 | 6.45 | 37.66 | 9.02 |
| C.M. | 37.64 | 19.093 | 37.78 | 5.83 | 37.88 | 8.38 |
| S.A. | 37.31 | 14.505 | 37.49 | 5.59 | 37.61 | 7.57 |
| L.S. | 37.16 | 10.795 | 37.40 | 5.58 | 37.80 | 8.48 |
| Mean ± | 37.34 | 13.246 | 37.58 | 5.97 | 37.79 | 8.45 |
| SE | 0.08 | 1.697 | 0.08 | 0.19 | 0.07 | 0.25 |
| p value | $p = 0.05$ | N.S. | N.S. | $0.001 < p < 0.01$ | N.S. | $0.01 < p < 0.02$ |

$p > .05$ N.S.

TABLE 5. Metabolic data of control and anorectic subjects

| | $\dot{V}O_2$ STPD ($ml \cdot min^{-1} \cdot kg^{-1}$) | | | | Respiratory Exchange Ratio (R) | | | |
|---|---|---|---|---|---|---|---|---|
| | | Exercise | | | | Exercise | | |
| Controls | Rest | 5 min | 10 min | 15 min | Rest | 5 min | 10 min | 15 min |
| D.C. | 3.6 | 19.0 | 20.3 | 19.4 | 0.81 | 0.98 | 0.91 | 0.94 |
| C.Mc. | 2.6 | 31.4 | 26.0 | 25.5 | 0.89 | 0.78 | 0.96 | 0.96 |
| E.G. | 2.8 | 22.5 | 22.9 | 22.0 | 0.89 | 0.92 | 0.85 | 0.84 |
| D.M. | 2.7 | 15.6 | 16.2 | 17.4 | 0.91 | 1.01 | 0.89 | 0.95 |
| S.D. | 3.4 | 26.4 | 28.6 | 28.8 | 0.75 | 0.79 | 0.79 | 0.81 |
| (n=5) | | | | | | | | |
| Mean ± | 3.02 | 22.98 | 22.80 | 22.62 | 0.85 | 0.90 | 0.88 | 0.90 |
| SE | 0.20 | 2.77 | 2.12 | 2.01 | 0.03 | 0.05 | 0.03 | 0.03 |
| Anorectics | | | | | | | | |
| L.E. | 3.8 | 24.4 | 25.5 | 23.9 | 0.69 | 0.84 | 0.81 | 0.81 |
| D.R. | 3.3 | 20.9 | 18.9 | 21.7 | 0.73 | 0.86 | 0.89 | 0.83 |
| C.M. | 4.2 | 19.6 | 20.9 | 21.0 | 0.85 | 0.98 | 0.91 | 0.89 |
| S.A. | 2.5 | 11.1 | 11.1 | 10.8 | 1.02 | 1.20 | 1.16 | 1.21 |
| L.S. | 2.0 | 17.6 | 17.7 | 17.8 | 0.91 | 1.13 | 1.13 | 1.13 |
| (n=5) | | | | | | | | |
| Mean ± | 3.16 | 18.72 | 18.82 | 19.04 | 0.84 | 1.00 | 0.98 | 0.97 |
| SE | 0.41 | 2.20 | 2.34 | 2.28 | 0.06 | 0.07 | 0.07 | 0.08 |
| p value | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. |

$p > 0.05$ N.S.

TABLE 6. $\dot{V}O_2$ and Power

| Controls (n=5) | Average $\dot{V}O_2$ During Exercise ($ml \cdot min^{-1} \cdot kg^{-1}$) | Work (kip) | Power (Watts) |
|---|---|---|---|
| D.C. | 19.6 | 1.25 | 73.5 |
| C.Mc. | 27.6 | 1.75 | 102.9 |
| E.G. | 22.5 | 1.35 | 79.4 |
| D.M. | 16.4 | 1.00 | 58.8 |
| S.D. | 27.9 | 1.25 | 73.5 |
| | $\dot{V}O_2 = 0.23$ (Watts) + 5.21 | r = 0.73 | |
| Anorectics (n=5) | | | |
| L.E. | 24.6 | 1.00 | 58.8 |
| D.R. | 20.5 | 0.83 | 48.8 |
| C.M. | 20.5 | 0.75 | 25.9 |
| S.A. | 11.0 | 0.44 | 44.1 |
| L.S. | 17.7 | 1.10 | 64.7 |
| | $\dot{V}O_2 = 0.24$ (Watts) + 7.47 | r = 0.70 | |

TABLE 7. Blood chemistries data

| | Glucose (mg %) | | Urea Nitrogen (mg%) | | Creatinine (mg%) | | Triglycerides (mg%) | | Lactic Acid (mg%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Controls | Pre-ex | Post-ex | Pre-ex | Post-ex | Pre-ex | Post-ex | Pre-ex | Post-ex | Pre-ex | Post-ex |
| D.C. | 87 | 95 | 17 | 16 | 0.9 | 0.7 | 79 | 79 | 7 | 17 |
| C.Mc. | 62 | 75 | 11 | 11 | 0.8 | 0.8 | 64 | 55 | 13 | 11 |
| E.G. | 75 | 77 | 19 | 19 | 1.0 | 1.0 | 110 | 123 | - | - |
| D.M. | 81 | 79 | 12 | 11 | 0.8 | 0.8 | 54 | 51 | 11 | 12 |
| S.D. | 72 | 78 | 18 | 16 | 0.8 | 0.8 | 52 | 79 | 5 | 4 |
| Anorectics | | | | | | | | | | |
| L.E. | 67 | 64 | 15 | 15 | 0.9 | 0.9 | 135 | 135 | 19 | 11 |
| D.R. | 67 | 66 | 16 | 15 | 1.0 | 0.9 | 85 | 80 | 7 | 21 |
| C.M. | 63 | 51 | 14 | 14 | 0.9 | 0.9 | 113 | 110 | 4 | 28 |
| S.A. | 82 | 69 | 15 | 15 | 0.9 | 0.9 | 306 | 195 | 13 | 28 |
| L.S. | 74 | 74 | - | - | 0.8 | 0.8 | 56 | 64 | 5 | 16 |

TABLE 8. Comparison of 2 methods for measuring body fat content in patients with aneorxia nervosa

| | Skinfold Thickness Method [1] | | | Body Density Method [2] | | | | |
|---|---|---|---|---|---|---|---|---|
| Anorectics (n=5) | Wt (kg) | Sum of Skinfolds (mm) | % fat [3] | Wt (kg) | Residual Volume (l) | Body Density | % fat [3] | Body Density Skinfold Ratio |
| L.E. | 46.0 | 38.8 | 7.7 | 45.099 | 0.56 | 1.067 | 8.1 | 1.05 |
| D.R. | 44.3 | 32.3 | 6.3 | 43.212 | 0.767 | 1.049 | 16.2 | 2.59 |
| C.M. | 38.0 | 23.6 | 4.7 | 37.112 | 1.411 | 1.062 | 10.4 | 2.21 |
| S.A. | 38.1 | 31.2 | 7.0 | 38.480 | 1.075 | 1.054 | 14.1 | 2.01 |
| L.S. | 44.7 | 41.5 | 8.6 | 44.468 | 1.16 | 1.062 | 10.4 | 1.21 |
| Mean ± | | | 6.9 | | | | 11.8 | 1.69 |
| SD | | | 1.5 | | | | 3.3 | 0.23 |

[1] After Anyan (2)

[2] After Keys & Brozek (42)

[3] $0.02 < p < 0.05$ by Student's paired t-test

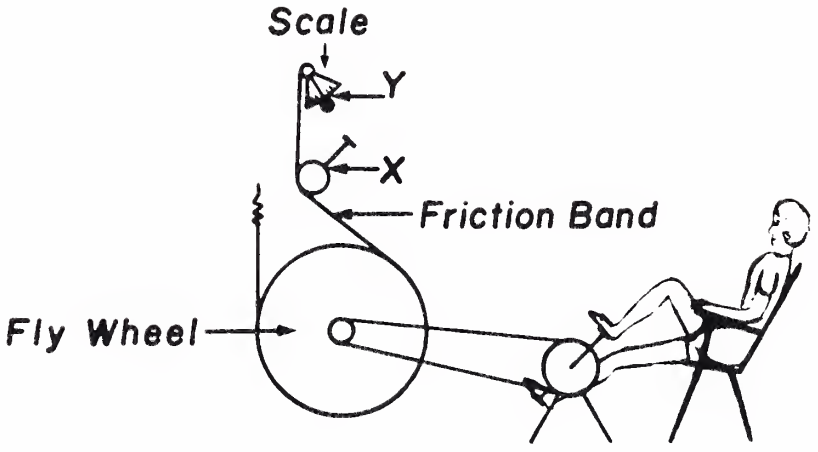


Fig. 1. Modified Monark cycle ergometer (after Bigland-Ritchie (6)). Adjustments in the tension imposed on the friction band around the flywheel of the ergometer were made at X, and registered on the scale at Y.

Fig. 2. Whitney mercury-in-Silastic strain gauge, used in measuring forearm blood flow by venous occlusion plethysomography.

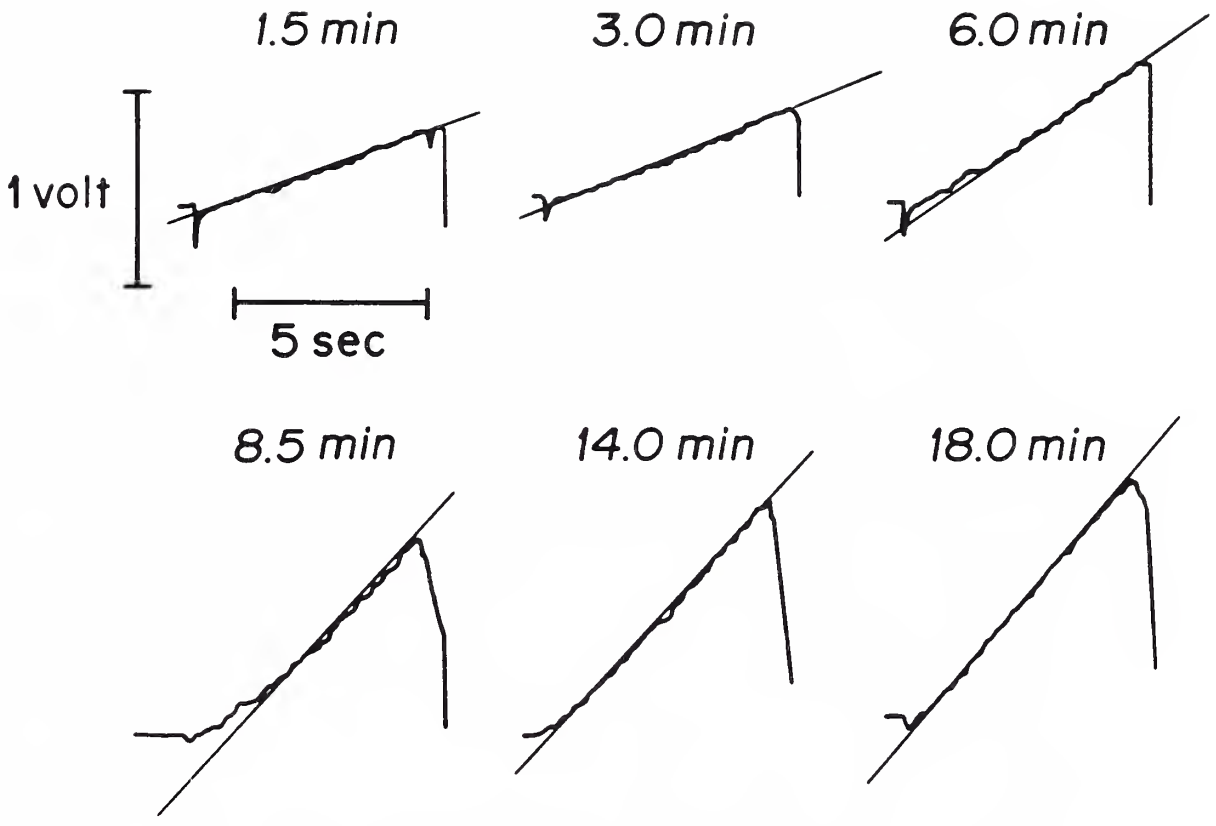


Fig. 3. Representative plethysmographic records (patient L.S.) with tangents fitted to estimate forearm blood flow. Time moved from right to left. Artifacts from the inflation of the venous occlusion cuff were seen at the beginnings of the tracings. Time represents minutes of exercise; increases in slope were noted with increased length of exercise.

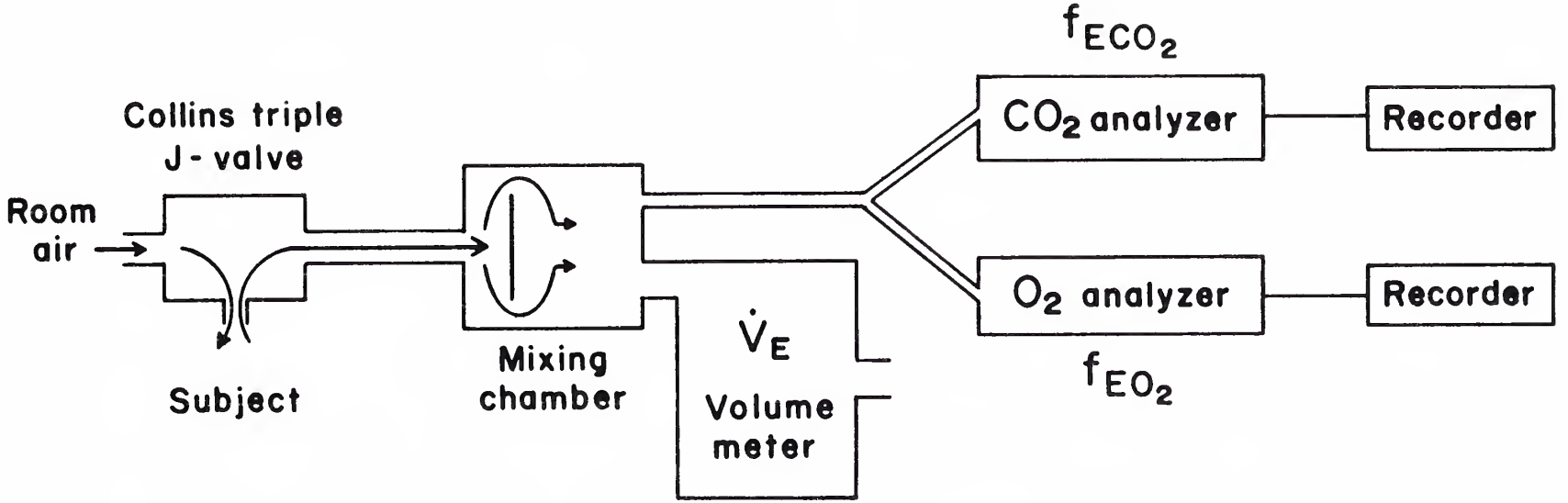


Fig. 4. Schematic of direction of air flow and gas analysis. A subject inspired room air through a Collins triple-J one-way valve and expired air was directed into a mixing chamber. Continuous sampling from the mixing chamber was for $O_2$ and $CO_2$ analysis. A volume meter recorded the volume of expired air which entered the mixing chamber.

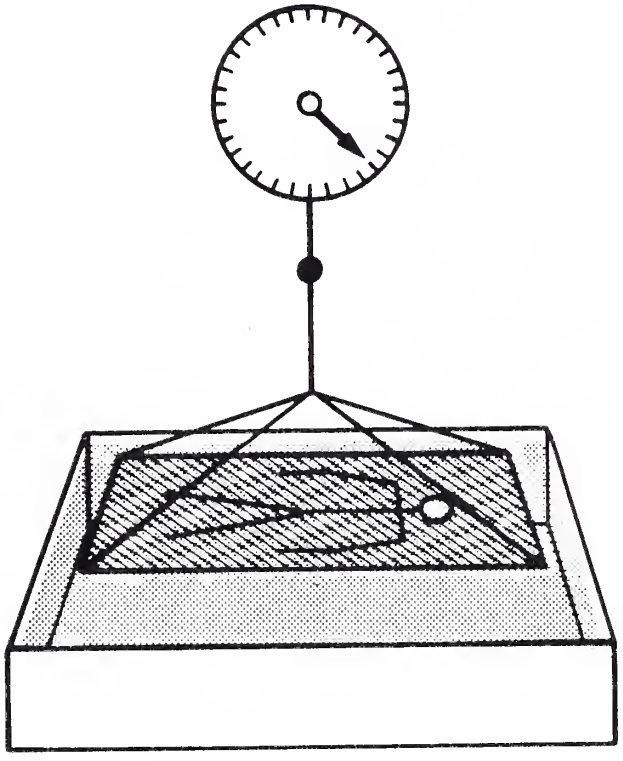

Fig. 5. Underwater weighing apparatus (after Ricci (63)) for estimation of specific gravity. A subject lay on a frame suspended from an autopsy-type scale. The frame was submerged in a Hubbard tank, the subject exhaled completely, and the weight was recorded.

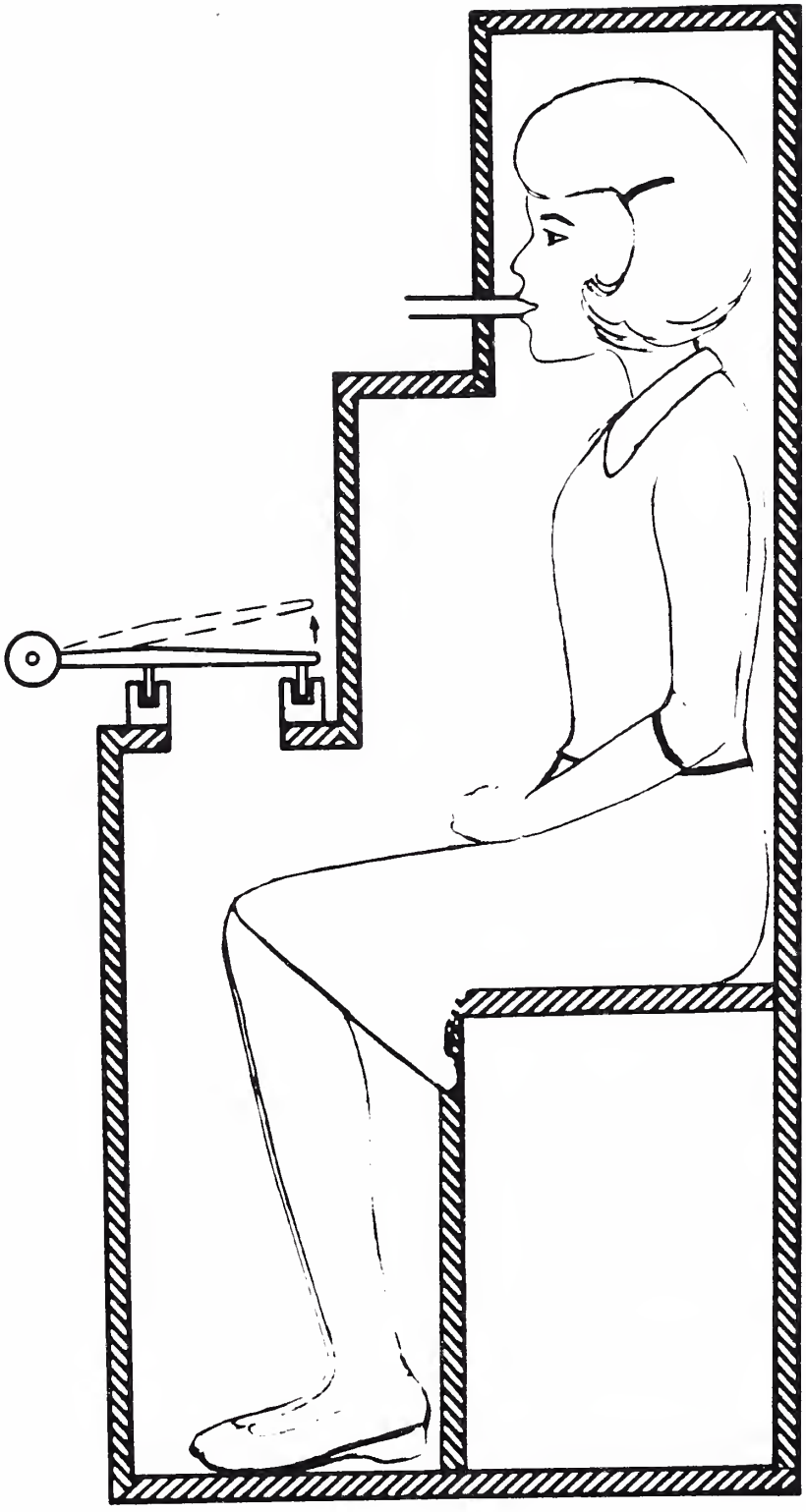

Fig. 6. Body volume plethysmograph for determination of residual lung volume. A subject sat in an air-tight box and breathed through a mouthpiece. As the subject changed volume, this volume of displaced gas was measured with a spirometer.

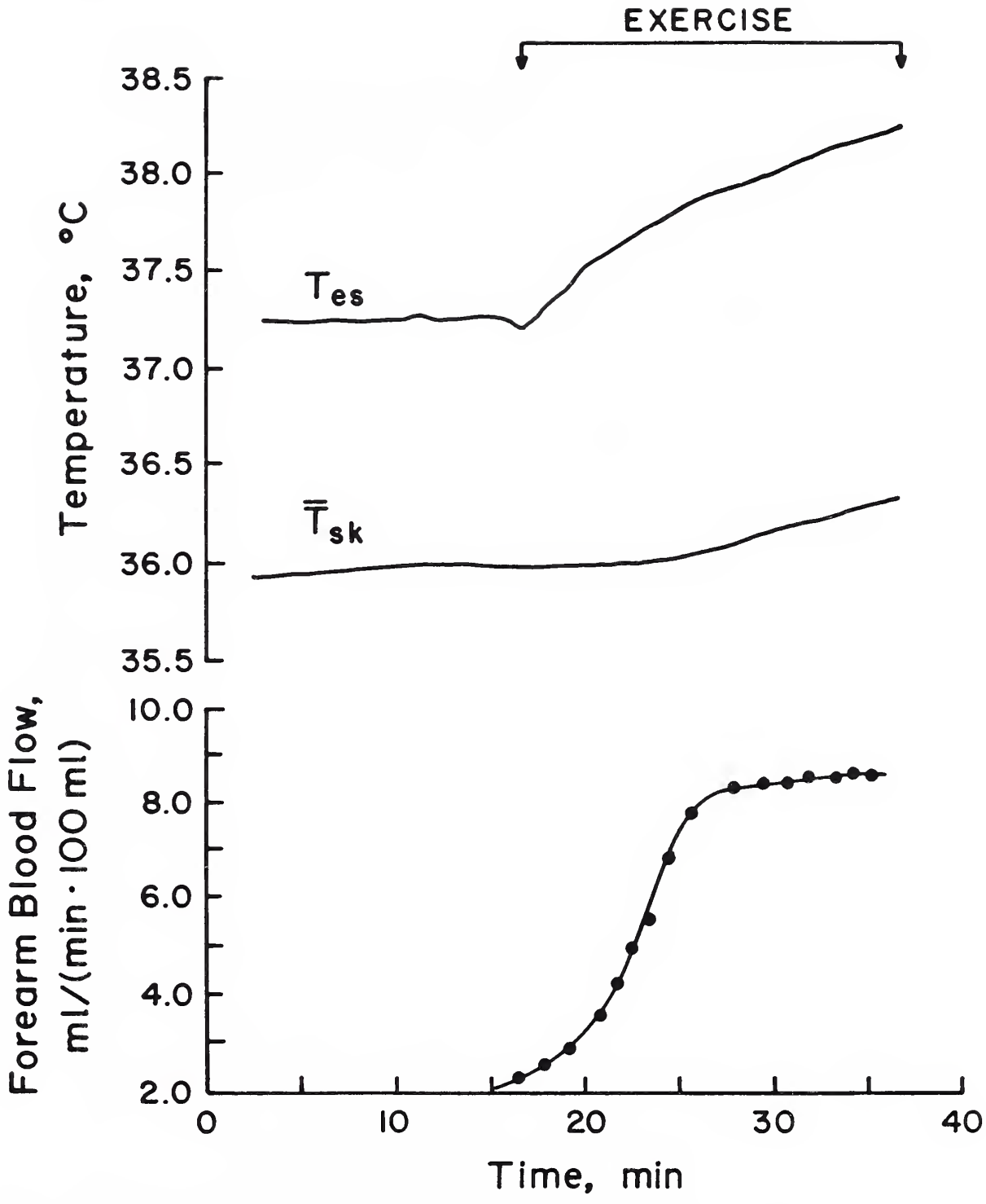


Fig. 7. Representative data (patient L.S.) of esophageal temperature ($T_{es}$), mean skin temperature ($T_{sk}$) and forearm blood flow relative to time in an ambient temperature of 33°C. Exercise intensity was between 40 and 50% $\dot{V}O_2$ max.

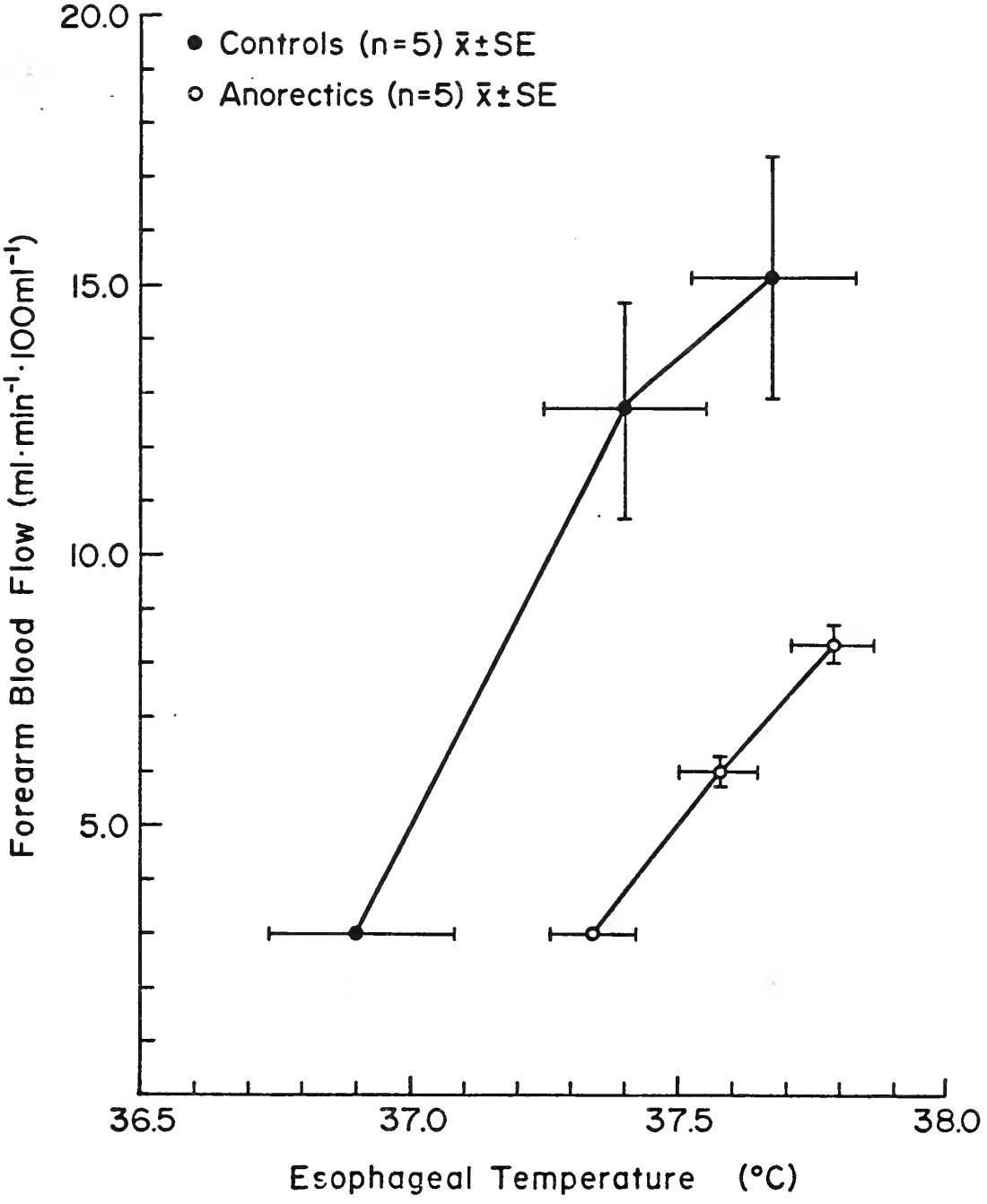


Fig. 8. Forearm blood flow as a function of esophageal temperature ($T_{es}$). Threshold for vasodilation was defined as the $T_{es}$ at which forearm blood flow is 3 $ml \cdot min^{-1} \cdot 100\ ml^{-1}$. Ambient temperature was 33°C. All data points were averaged for mean $T_{es}$ and mean $\overline{BF}$ and the steady state $T_{es}$ and mean $\overline{BF}$ averaged data points collected during the last 5 minutes of exercise.

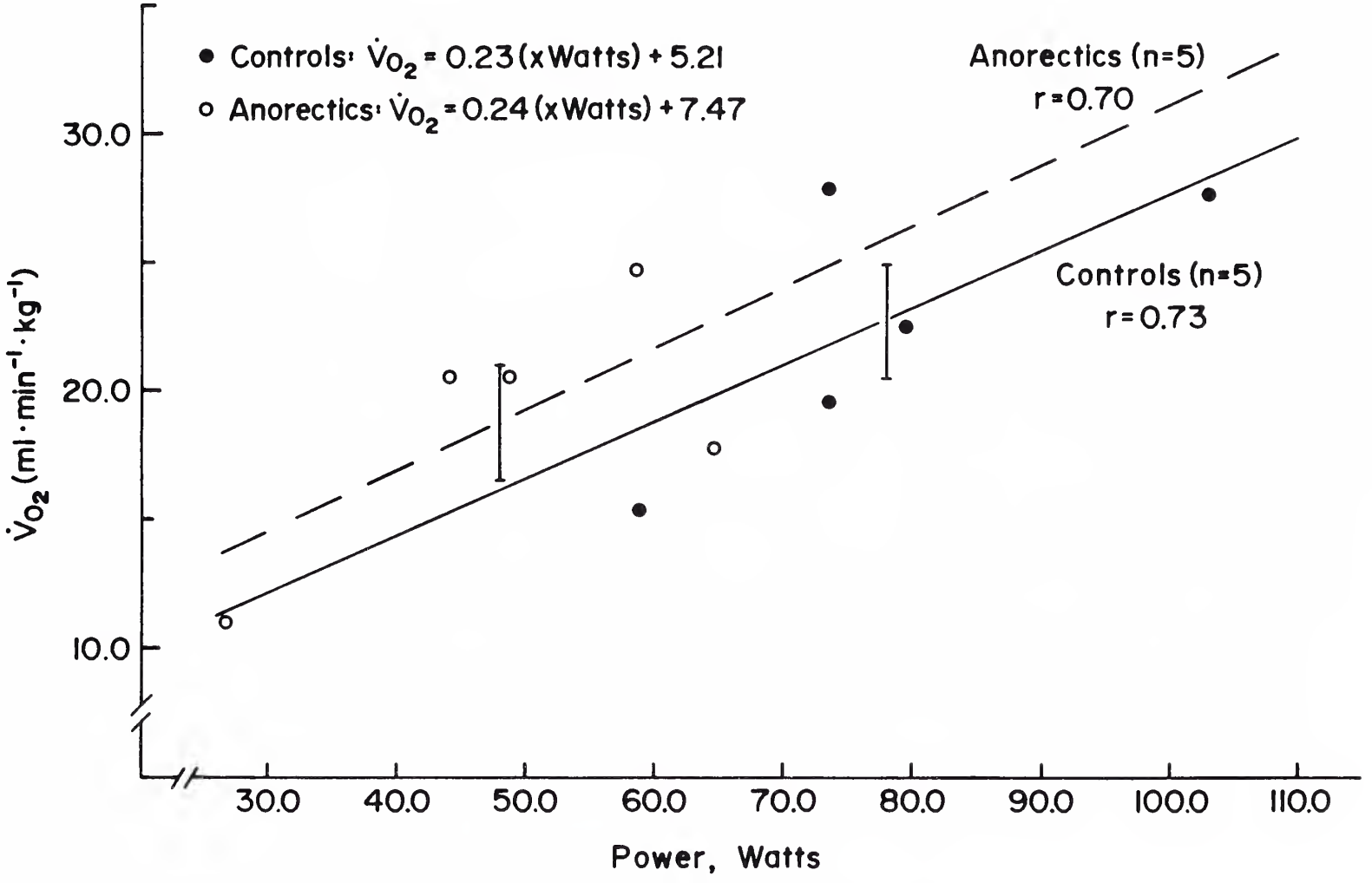


Fig. 9. $\dot{V}O_2$ Oxygen uptake ($\dot{V}O_2$) as a function of power during exercise at an intensity between 40 and 50% $\dot{V}O_2$ max. Ambient temperature was 33°C. Standard error bars are drawn around the means of each group.

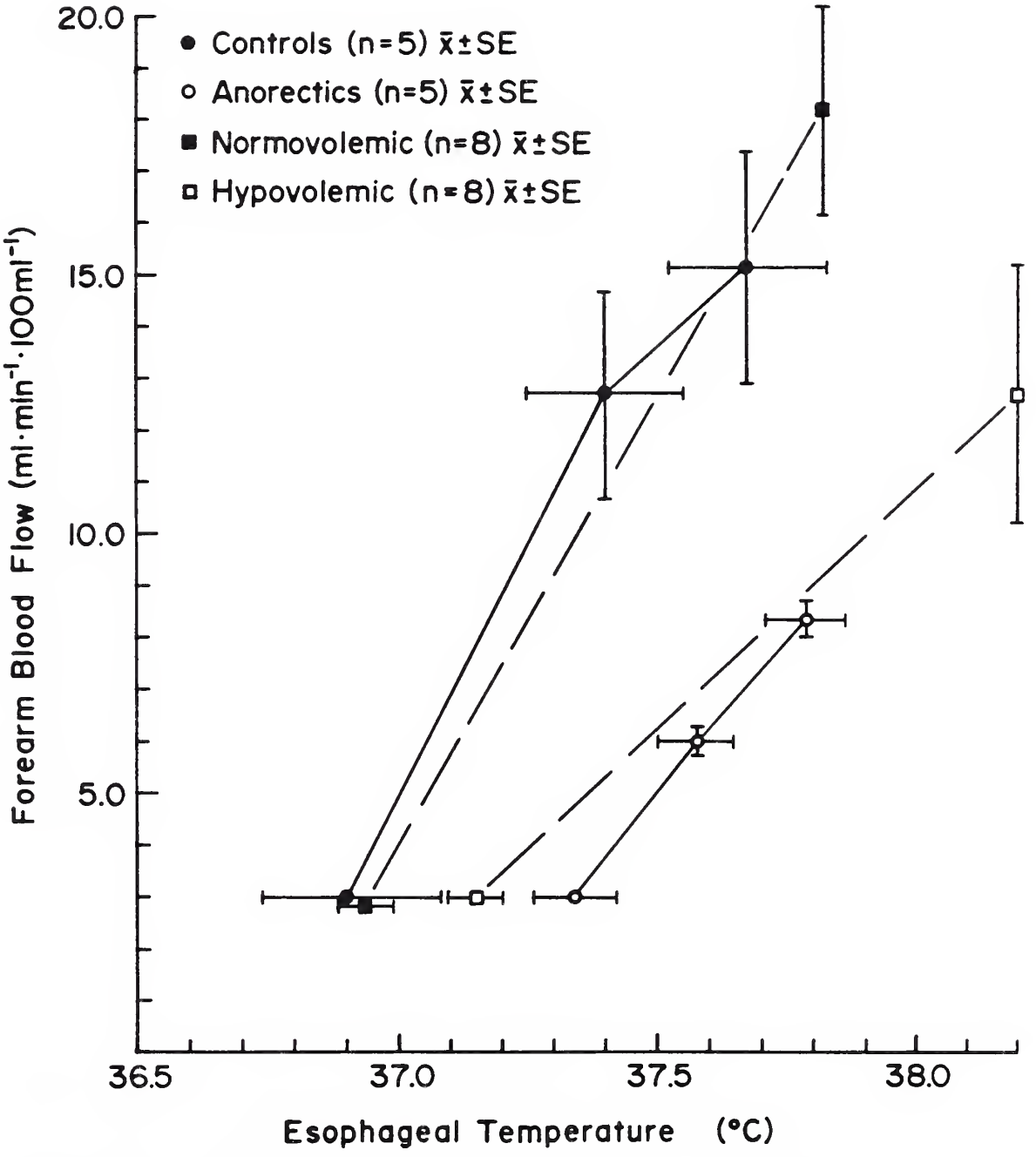


Fig. 10. Forearm blood flow as a function of esophageal temperature ($T_{es}$) with data from normovolemic and hypovolemic experiments (59) superimposed to illustrate the similarities in the vasodilation threshold $T_{es}$ and BF:$T_{es}$ relationship between the anorectic patients and hypovolemic experiments.

YALE MEDICAL LIBRARY

Manuscript Theses

Unpublished theses submitted for the Master's and Doctor's degrees and deposited in the Yale Medical Library are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but passages must not be copied without permission of the authors, and without proper credit being given in subsequent written or published work.

This thesis by has been used by the following persons, whose signatures attest their acceptance of the above restrictions.

| NAME AND ADDRESS | DATE |
| --- | --- |
| James R. Coleman | |